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Enantioselective Synthesis of 4,5-Dihydropyrroles via Domino Ring-Opening Cyclization (DROC) of *N*-Activated Aziridines with Malononitrile

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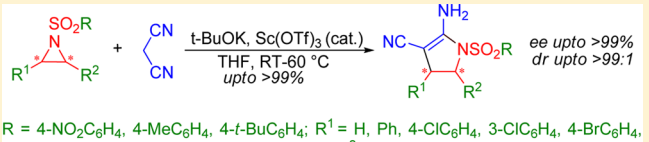
Supporting Information

ABSTRACT: An efficient and practical strategy for the synthesis of highly functionalized racemic and non-racemic 4,5-dihydropyrroles via domino ring-opening cyclization (DROC) of activated aziridines with malononitrile in excellent yield and stereoselectivity is described. The reaction serves as a tool for the synthesis of a large variety of substituted 4,5-dihydropyrroles in enantiomerically pure forms.



R = 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-*t*-BuC_6H_4; R^1 = H, Ph, 4-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-*t*BuC_6H_4 4-$OAcC_6H_4$; R^2 = H, Me, *i*Pr, Bn, *n*-Pr, allyl, CH_2OTBS

INTRODUCTION

Dihydropyrroles are an important class of heterocyclic compounds found as a functional core of various natural products and pharmaceutical agents.[1] Moreover, some of them serve as excellent precursors for various nitrogen-containing heterocyclic compounds of synthetic and biological interest.[2] A number of attractive routes have been designed for the synthesis of these heterocycles.[3] Although many efforts have been devoted for the synthesis of 2,5- and 2,3-dihydropyrroles,[3] comparatively less attention has been paid to 4,5-dihydropyrroles[4] despite their numerous applications in natural product chemistry[1a,c,2a] and spin trapping experiments.[5]

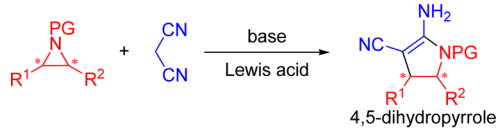
Aziridines[6−8] have been utilized as one of the most suitable building blocks for the synthesis of various nitrogen containing heterocyclic compounds.[7] Surprisingly, they have been less explored for the synthesis of substituted dihydropyrroles.[9,10] To the best of our knowledge there is no report for the synthesis of enantiomerically pure 4,5-dihydropyrroles from aziridines. Over the years, we have been involved in S_N2-type ring-opening followed by alkylative cyclization of chiral aziridines[8] for the synthesis of enantioenriched targets of contemporary interest.[8a,c−h] We realized that chiral substituted 4,5-dihydropyrroles could easily be synthesized via ring-opening followed by cyclization of chiral aziridines with malononitrile in a domino fashion.

We have developed a simple and highly efficient strategy for the stereoselective synthesis of 4,5-dihydropyrroles with a synthetically important enaminonitrile moiety[11] via a Lewis acid (LA) catalyzed domino ring-opening cyclization (DROC) of substituted aziridines with malononitrile for the first time (Scheme 1). Herein, we present our results in detail.

RESULTS AND DISCUSSION

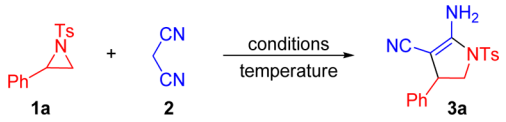
Initially, we carried out a reaction of 2-phenyl-*N*-tosylaziridine **1a** with 1.5 equiv of malononitrile **2** using NaH as the base in THF at room temperature (Table 1), and after completion of the reaction (4.5 h), the corresponding 4,5-dihydropyrrole **3a** was obtained in 39% yield. In another set of experiments, when the reaction mixture was heated at 60 °C, the starting material was

Scheme 1. Stereoselective Synthesis of 4,5-Dihydropyrroles via DROC of Aziridines with Malononitrile



R^1 = Ar, H; R^2 = H, alkyl; PG (protecting group) = $ArSO_2$

Table 1. Optimization Study



entry	conditions	temp	time (h)	yield[a] (%)
1	NaH, THF	RT	4.5	39
2	NaH, THF	RT−60 °C	2.5	42
3	NaH, $Cu(OTf)_2$,[b] THF	RT−60 °C	1.0	58
4	NaH, $Sc(OTf)_3$,[b] THF	RT−60 °C	0.5	94
5	NaH, $Yb(OTf)_3$,[b] THF	RT−60 °C	1.0	86
6	NaH, $Zn(OTf)_2$,[b] THF	RT−60 °C	1.75	86
7	NaH, $Ti(OiPr)_4$,[b] THF	RT−60 °C	1.25	77
8	*t*-BuOK, $Sc(OTf)_3$,[b] THF	RT−60 °C	0.5	97
9	*t*-BuOK, $Sc(OTf)_3$,[b] THF	RT	1.5	97
10	*t*-BuOK, THF	RT−60 °C	2.0	45

[a]Yields after column chromatographic purification. [b]20 mol % of LA catalyst was used.

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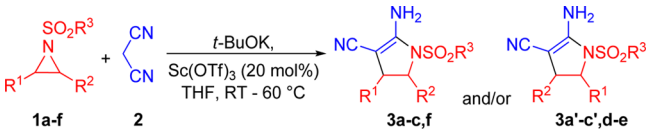
fully consumed in 2.5 h without any appreciable improvement in the yield of **3a**.

To find out the optimum reaction conditions (shorter reaction time and maximum yield), various Lewis acid catalysts and bases were screened for the DROC of **1a** with **2**, and the results are shown in Table 1. The best result was obtained using $Sc(OTf)_3$ as the LA and *t*-BuOK as the base; **3a** was produced in 97% yield (Table 1, entry 8). Having the optimized reaction condition in hand, we intended to apply our protocol for the synthesis of various substituted 4,5-dihydropyrroles (Table 2). The product

Table 2. Scope of the Reaction with various Monosubstituted *N*-Sulfonyl Aziridines



1a-f 2 3a-c,f 3a'-c',d-e

entry	aziridine	product(s)	yield[a] (%)
1	**1a**: $R^1 = C_6H_5$, R^2 = H, R^3 = 4-MeC_6H_4	**3a** + **3a′**	97[b,c]
2	**1b**: R^1 = 3-ClC_6H_4, R^2 = H, R^3 = 4-MeC_6H_4	**3b** + **3b′**	90[b,d]
3	**1c**: $R^1 = C_6H_5$, R^2 = H, R^3 = 4-*t*-BuC_6H_4	**3c** + **3c′**	>99[b,e]
4	**1d**: R^1 = *i*Pr, R^2 = H, R^3 = 4-MeC_6H_4	**3d**	92
5	**1e**: R^1 = *n*-Oct, R^2 = H, R^3 = 4-MeC_6H_4	**3e**	99
6	**1f**: $R^1 = R^2 = -(CH_2)_4$, R^3 = 4-MeC_6H_4	**3f**	75

[a]Yields of isolated products after column chromatographic purification. [b]Combined yields of both the regioisomers. [c]**3a**:**3a′** 8:1. [d]**3b**:**3b′** 3:1. [e]**3c**:**3c′** 5:1 (determined from ^{1}H NMR of the crude reaction mixture).

3a was obtained as a mixture of regioisomers (**3a** and **3a′**) with high regioisomeric ratio (8:1) (entry 1). Similar DROC of aziridines **1b** and **1c** with **2** produced the corresponding dihydropyrroles **3b** (along with **3b′**) and **3c** (along with **3c′**), respectively, in excellent yields (entry 2, Table 2). Formation of the minor regioisomer is probably due to the partial attack of the malononitrile at the less substituted position of aziridines **1a**−**c**. When alkyl aziridines **1d,e** were used as the substrates, the corresponding 4,5-dihydropyroles **3d,e** were obtained in excellent yields as a single regioisomer via the attack of the nucleophile at the less sterically hindered position of the aziridines (entry 4 and 5). Compounds of the type **3e** possessing a hydrophilic head (-NH_2 group) and a hydrophobic tail are of both industrial (surfactants) and biological (lipid bilayer of cell membranes) importance. The DROC of cyclohexene aziridine **1f** with malononitrile was found to be extremely efficient, and the corresponding fused 4,5-dihydropyrrole **3f** was obtained as a single diastereomer. To the best of our knowledge, this is the first report for the synthesis of fused dihydropyrrole with synthetically explorable enamino-nitrile functionality.

Since *N*-nosylaziridines are more reactive than *N*-tosylaziridines and also the nosyl group is easily removable,[12] we explored DROC of 2-aryl-*N*-nosylaziridines with malononitrile **2**. When 2-phenyl-*N*-nosylaziridine **1g** was reacted with malononitrile, the corresponding dihydropyrole **3g** was obtained in excellent yield as a single regioisomer after column chromatographic purification.[13] Encouraged by this result, a number of substituted 2-aryl-*N*-nosylaziridines were studied for DROC with malononitrile, and in all the cases the corresponding 4,5-dihydropyrroles were obtained in excellent yields (Table 3). Various haloaryl, especially fluoroaryl, substituted *N*-nosylaziridines were reacted efficiently with malononitrile to afford the corresponding dihydropyrroles in excellent yields (entry 2−5). It is needless to mention that a fluoro substituent on the aromatic ring had found numerous applications in the pharmaceutical industry.[14]

Interestingly, when **1n** was reacted with malononitrile under optimized reaction condition, the corresponding deacetylated product **3n** was obtained probably due to LA catalyzed hydrolysis of the acetyl group under the reaction condition.

To broaden the scope of our protocol, it was extended further for the synthesis of chiral 4,5-dihydropyrroles. For this purpose enantiomerically pure alkyl (isopropyl, benzyl, methyl, etc.) substituted aziridines (*S*)-**1d,o,p** and 2-phenyl-*N*-nosylaziridine (*R*)-**1g** were employed as the substrates (Table 4). The DROC of chiral aziridines (*S*)-**1d,o,p** with malononitrile produced the corresponding dihydropyroles in enantiomerically pure forms as a single regioisomer (Table 4). Similarly, when chiral 2-phenyl-*N*-nosylaziridine (*R*)-**1g** was used as the substrate, the corresponding dihydropyrrole (*R*)-**3g** was obtained in enantiomerically pure form (entry 5).

The strategy was further extended to 2,3-disubstituted chiral aziridines[7b] to obtain highly substituted chiral 4,5-dihydropyrroles (Table 5). When *trans*-2-phenyl-3-*n*-propyl-*N*-tosylaziridine (2*S*,3*S*)-**1q** was reacted with malononitrile, the corresponding *cis*-dihydropyrrole (4*S*,5*S*)-**3q** was obtained in quantitative yield as a single diastereomer. A similar result was obtained with (2*S*,3*S*)-**1r** as the substrate, and the corresponding product (4*S*,5*S*)-**3r** was produced in diastereomerically pure form with quantitative yield. The *cis*-stereochemistry of the products **3r**−**s** were determined by NOE experiments.[15]

In the compound **3r** the allylic protons H^a and H^b showed NOE enahancement with the aromatic ortho proton (H^{ortho}), whereas there was no such NOE relation of H^d (benzylic proton) with H^a and/or H^b, confirming the *cis* relationship of the phenyl and allyl groups (Figure 1).

With a view to synthesizing highly functionalized dihydropyrroles suitable for further synthetic manipulations into various other motifs, we studied the DROC of *trans* aziridine **1s** with malononitrile. As expected, the product **3s** was obtained in excellent yield as a single diastereomer with 4,5-*cis* appendages. Compound **3s** can be transformed into various other functional groups via functional group interconversion of the TBS ether group (Scheme 2).

We believe that the reaction follows an S_N2-type pathway as proposed by us earlier.[8] The LA activated aziridine intermediate (**A**) undergoes nucleophilic attack by malononitrile anion to generate another intermediate **B**, which upon intramolecular cyclization and quenching by aqueous NH_4Cl followed by tautomerization provides the dihydropyrrole products **3** (Scheme 3).

For wider applicability of the developed strategy as a general methodology, the dihydropyrrole **3g** was denosylated[6l,8a] to the corresponding *N*-unsubstituted product **4**[15] following literature reports (Scheme 4).

CONCLUSION

In conclusion, we have developed a very simple, efficient, and practical strategy for the synthesis of highly functionalized 4,5-dihydropyrroles both in racemic as well as enantiopure forms via a LA catalyzed DROC of activated aziridines with malononitrile.

EXPERIMENTAL SECTION

General Experimental. The progress of the reaction was monitored via thin layer chromatography (TLC) performed using silica gel 60 F_{254} precoated plates, and the spots were visualized using a UV lamp or I_2

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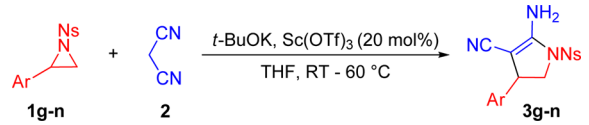
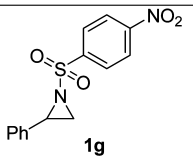
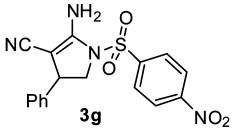
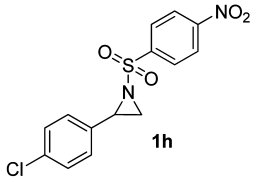
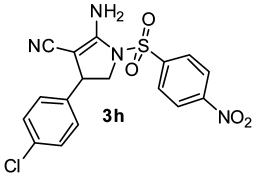
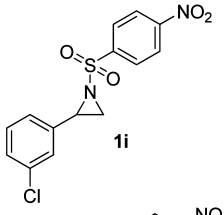
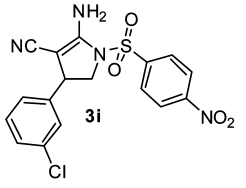
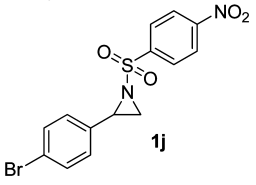
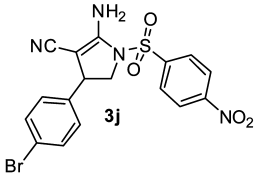
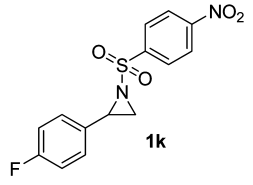
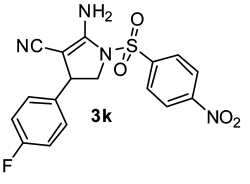
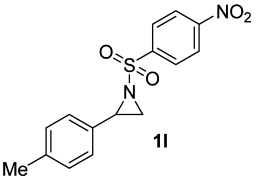
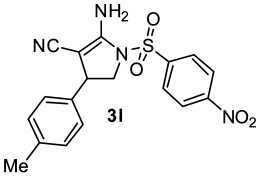
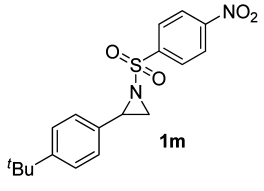
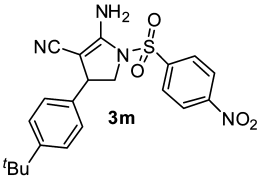
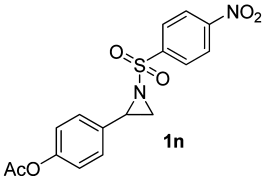
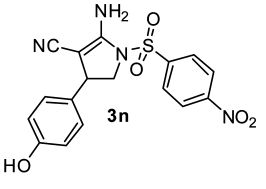
Table 3. Scope of the Reaction with Various Substituted *N*-Nosyl Aziridines



Entry	Ar (Aziridine)	Products	Yield[a] (%)
1	 **1g**	 **3g**	88
2	 **1h**	 **3h**	85
3	 **1i**	 **3i**	89
4	 **1j**	 **3j**	85
5	 **1k**	 **3k**	87
6	 **1l**	 **3l**	89
7	 **1m**	 **3m**	84
8	 **1n**	 **3n**	88

[a]Yields of isolated products after column chromatographic purification.

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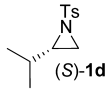
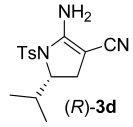
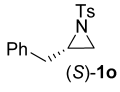
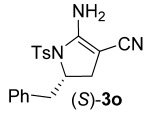
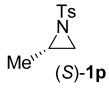
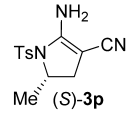
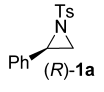
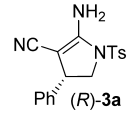
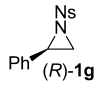
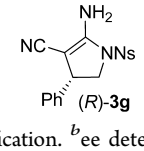
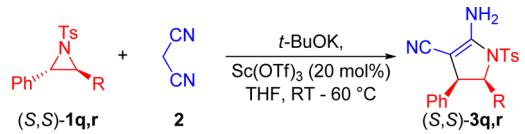
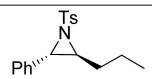
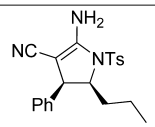
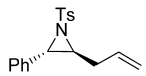
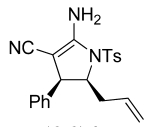
Table 4. Synthesis of Chiral 4,5-Dihydropyrroles

Entry	Aziridine	Product	Yield[a] (%)	ee[b] (%)
1	 (*S*)-**1d**	 (*R*)-**3d**	92	>99
2	 (*S*)-**1o**	 (*S*)-**3o**	95	>99
3	 (*S*)-**1p**	 (*S*)-**3p**	92	>99
4	 (*R*)-**1a**	 (*R*)-**3a**	97[c]	ND[d]
5	 (*R*)-**1g**	 (*R*)-**3g**	88	>99

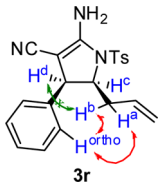
[b]Yields of isolated products after column chromatographic purification. [b]ee determined by chiral HPLC (see Supporting Information for details). [c]Combined yield of both the regioisomers. [d]ee could not be determined as the compound was obtained as an inseparable mixture of regioisomers (8:1).

Table 5. Synthesis of Highly Substituted Chiral 4,5-Dihydropyrroles from 2,3-Disubstituted Chiral Aziridines



Entry	Aziridine	Product	Yield[a] (%)	dr
1	 (*S*,*S*)-**1q**	 (*S*,*S*)-**3q**	>99	>99:1
2	 (*S*,*S*)-**1r**	 (*S*,*S*)-**3r**	>99	>99:1

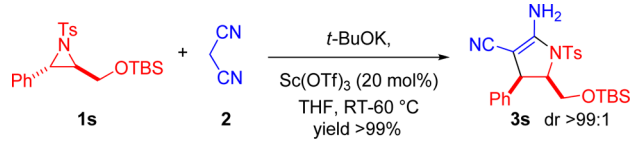
[a]Yields of isolated products after column chromatographic purification.



3r

Figure 1. NOE experiment for the determination of stereochemistry of **3r**.

Scheme 2. Synthesis of Highly Functionalized 4,5-Dihydropyrroles



stain. Silica gel 230−400 mesh size was used for flash column chromatography with a combination of ethyl acetate and petroleum ether as eluent. Unless otherwise noted, all reactions were carried out in oven-dried glassware under nitrogen atmosphere using anhydrous solvents. Wherever appropriate, all reagents were purified prior to use following Perrin and Armarego guidelines.[16] Monosubstituted *N*-Ns aziridines were synthesized according to a known literature report.[17]

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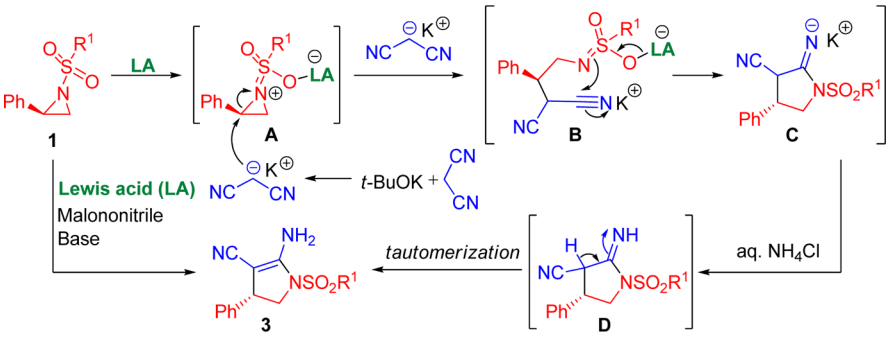
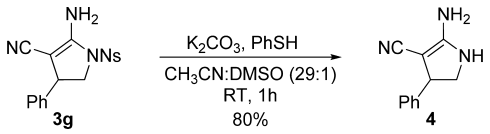
Scheme 3. Proposed Mechanism



Scheme 4. Denosylation of 4,5-Dihydropyrrole



Monosubstituted *N*-Ts aziridines[18] and disubstituted aziridines[8b] were prepared from the corresponding amino alcohols following earlier reports. All commercial reagents were used as received without further purification unless mentioned. ^{1}H NMR spectra were recorded on 400 or 500 MHz instruments, and the chemical shifts were recorded in parts per million (ppm, δ) taking tetramethyl silane (δ 0.00) as the internal standard. Splitting patterns of ^{1}H NMR are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m), etc. ^{13}C NMR spectra were recorded on 100 or 125 MHz instruments. HRMS were obtained using (ESI) mass spectrometer (TOF). IR spectra of liquid compounds were recorded as neat, whereas KBr plates were used for solid compounds. Melting points were measured using hot stage apparatus and are uncorrected. Enantiomeric excess (ee) was determined by HPLC using Chiralpak AS-H and Chiralcel OD-H 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 solvent) at 25 °C.

Experimental Procedure. To a suspension of *t*-BuOK (1.5 equiv) in THF (2.0 mL) was added malononitrile (1.5 equiv) was added at room temperature under nitrogen atmosphere. Subsequently solutions of *N*-sulfonyl aziridine (100 mg, 1.0 equiv) and Sc(OTf)$_3$ (20 mol %) in THF were added to the reaction mixture. Then the reaction mixture was stirred at 60 °C for the appropriate time. After complete consumption of the starting material (monitored by TLC), the reaction was quenched with saturated aqueous NH_4Cl solution (1.0 mL). After separating the organic phase, the aqueous phase was extracted with ethyl acetate (3 × 1.0 mL), and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to give pure 4,5-dihydropyrroles.

Spectral Data. 2-Amino-4-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3a). The general method described above was followed when **1a** (100 mg, 0.366 mmol) was reacted with malononitrile (35 μL, 0.549 mmol) in the presence of *t*-BuOK (62 mg, 0.549 mmol) using 20 mol % of Sc(OTf)$_3$ (36 mg, 0.073 mmol) at 60 °C for 30 min to afford **3a** (120 mg, 0.354 mmol) as a white frothy solid in 97% yield as a mixture of regioisomers (ratio 8:1): R_f 0.44 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3448, 3362, 2963, 2190, 1646, 1594, 1469, 1454, 1425, 1355, 1276, 1164, 1088, 1043, 814, 770, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.52 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.97 (dd, *J* = 10.1, 5.2 Hz, 1H), 4.11 (t, *J* = 10.4 Hz, 3H), 5.67 (s, 2H), 6.83−6.86 (m, 2H), 7.14−7.18 (m, 3H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 42.8, 56.9, 65.7, 118.0, 126.9, 127.5, 127.8, 128.9, 130.4, 132.7, 141.7, 145.6, 155.1; HRMS (ESI) calcd for $C_{18}H_{17}N_3O_2S$ (M + H)$^+$ 340.1120, found 340.1124. For (*R*)-**3a**: $[\alpha]^{25}_D$ = −35.1 (*c* 0.256, $CHCl_3$); enantioselectivity of (*R*)-**3a** could not be determined as it is an inseparable mixture of regioisomers.

2-Amino-4-(3-chlorophenyl)-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3b). The general method described above was followed when **1b** (100 mg, 0.325 mmol) was reacted with malononitrile (31 μL, 0.487 mmol) in the presence of *t*-BuOK (55 mg, 0.487 mmol) using 20 mol % of Sc(OTf)$_3$ (36 mg, 0.073 mmol) at 60 °C for 30 min to afford **3b** (110 mg, 0.292 mmol) as a white frothy solid in 90% yield as a mixture of regioisomers (ratio 3:1): R_f 0.38 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3458, 3357, 2923, 2854, 2189, 1637, 1594, 1471, 1431, 1359, 1273, 1241, 1163, 1091, 1047, 809, 785, 743; ^{1}H NMR of the major regioisomer (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.49 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.94 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.14 (t, *J* = 10.4 Hz, 3H), 5.59 (s, 2H), 6.76−6.79 (m, 2H),7.09−7.26 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR of the major regioisomer (125 MHz, $CDCl_3$) δ 21.8, 42.5, 56.7, 63.5, 117.7, 126.8, 127.4, 127.7, 127.8, 130.3, 130.4, 132.6, 134.9, 144.0, 145.9, 155.3; HRMS (ESI) calcd for $C_{18}H_{16}ClN_3O_2S$ (M − H)$^-$ 372.0574, found 372.0577.

2-Amino-1-(4-*tert*-butylphenylsulfonyl)-4-phenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3c). The general method described above was followed when **1c** (100 mg, 0.317 mmol) was reacted with malononitrile (30 μL, 0.476 mmol) in the presence of *t*-BuOK (53 mg, 0.476 mmol) using 20 mol % of Sc(OTf)$_3$ (31 mg, 0.063 mmol) at 60 °C for 30 min to afford **3c** (120 mg, 0.315 mmol) as a thick liquid in >99% yield as a mixture of regioisomers (ratio ∼4:1): R_f 0.38 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3447, 3365, 2964, 2870, 2190, 1647, 1592, 1470, 1427, 1358, 1264, 1199, 1167, 1113, 1085, 1045, 878, 799, 735, 700, 630; ^{1}H NMR of the major regioisomer (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.53 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.99 (dd, *J* = 10.3, 5.4 Hz, 1H), 4.14 (t, *J* = 10.8 Hz, 3H), 5.66 (s, 2H), 6.83−6.85 (m, 2H),7.14−7.28 (m, 3H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR of the major regioisomer (125 MHz, $CDCl_3$) δ 31.1, 35.5, 42.7, 56.9, 65.7, 118.1, 126.8, 126.9, 127.6, 127.8, 128.9, 132.6, 141.8, 155.1, 158.5; HRMS (ESI) calcd for $C_{21}H_{23}N_3O_2S$ (M + H)$^+$ 382.1589, found 382.1583.

2-Amino-4-isopropyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3d). The general method described above was followed when **1d** (100 mg, 0.418 mmol) was reacted with malononitrile (40 μL, 0.627 mmol) in the presence of *t*-BuOK (70 mg, 0.627 mmol) using 20 mol % of Sc(OTf)$_3$ (41 mg, 0.084 mmol) at 60 °C for 30 min to afford **3d** (118 mg, 0.386 mmol) as a white solid in 92% yield; mp 142−144 °C; R_f 0.41 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3459, 3364, 2961, 2925, 2854, 2190, 1729, 1650, 1596, 1463, 1421, 1359, 1294, 1264, 1188, 1166, 1089, 1022, 873, 814, 735, 706, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−0.92 (m, 6H), 2.15−2.31 (m, 3H), 2.47 (s, 3H), 3.81−3.86 (m, 1H), 5.38 (s, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 18.2, 21.8, 26.8, 32.9, 61.5, 66.5, 118.4, 127.4, 130.3, 134.0, 145.3, 154.8; HRMS (ESI) calcd for $C_{15}H_{19}N_3O_2S$ (M + H)$^+$ 306.1276, found 306.1275.

For (*R*)-**3d** $[\alpha]^{25}_D$ = +159.3 (*c* 0.203, $CHCl_3$); er >99:1, enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−isoproanol 95:5, flow rate = 1.0 mL/min; t_R = 51.50 min.

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2-Amino-5-octyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3e). The general method described above was followed when **1e** (100 mg, 0.323 mmol) was reacted with malononitrile (31 μL, 0.485 mmol) in the presence of *t*-BuOK (54 mg, 0.485 mmol) using 20 mol % of $Sc(OTf)_3$ (32 mg, 0.065 mmol) at 60 °C for 1.0 h to afford **3e** (120 mg, 0.320 mmol) as a white solid in 99% yield; mp 80−82 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3443, 3347, 2925, 2854, 2188, 1649, 1604, 1465, 1411, 1347, 1305, 1162, 1088, 1020, 990, 813, 707, 663, 592; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.28−1.81 (m, 14H), 2.13 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.42−2.48 (m, 1H), 2.47 (s, 3H), 3.89−3.95 (m, 1H), 5.38 (s, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.8, 22.8, 24.4, 29.3, 29.5, 29.6, 31.2, 31.9, 36.6, 60.5, 62.0, 118.6, 127.3, 130.3, 134.2, 145.2, 154.4; HRMS (ESI) calcd for $C_{20}H_{29}N_3O_2S$ $(M + H)^+$ 376.2059, found 376.2057.

2-Amino-1-tosyl-3a,4,5,6,7,7a-hexahydro-1*H*-indole-3-carbonitrile (3f). The general method described above was followed when **1f** (100 mg, 0.398 mmol) was reacted with malononitrile (38 μL, 0.597 mmol) in the presence of *t*-BuOK (67 mg, 0.597 mmol) using 20 mol % of $Sc(OTf)_3$ (39 mg, 0.079 mmol) at 60 °C for 30 min to afford **3f** (95 mg, 0.299 mmol) as a white solid in 75% yield; mp 152−154 °C; R_f 0.40 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3444, 3359, 3243, 3194, 2937, 2861, 2186, 1636, 1581, 1494, 1447, 1415, 1368, 1307, 1274, 1230, 1213, 1188, 1166, 1140, 1122, 1089, 1042, 1019, 967, 887, 835, 814, 779, 765, 736, 706, 662, 584; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98−1.09 (m, 1H), 1.17−1.30 (m, 2H), 1.63−1.73 (m, 2H), 1.86−1.89 (m, 2H), 2.00−2.05 (m, 1H), 2.37−2.60 (m, 2H), 2.48 (s, 3H), 5.70 (s, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 24.9, 25.0, 29.1, 30.7, 45.2, 65.5, 70.7, 118.1, 127.9, 130.3, 134.3, 145.5, 157.0; HRMS (ESI) calcd for $C_{16}H_{19}N_3O_2S$ $(M + H)^+$ 318.1276, found 318.1277.

2-Amino-1-(4-nitrophenylsulfonyl)-4-phenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3g). The general method described above was followed when **1g** (100 mg, 0.329 mmol) was reacted with malononitrile (31 μL, 0.493 mmol) in the presence of *t*-BuOK (55 mg, 0.493 mmol) using 20 mol % of $Sc(OTf)_3$ (32 mg, 0.066 mmol) at 60 °C for 5 min to afford **3g** (107 mg, 0.289 mmol) as a yellow solid in 88% yield; color changes to brown at 150 °C; R_f 0.41 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3450, 3321, 3266, 3219, 3108, 2924, 2193, 1651, 1595, 1532, 1496, 1457, 1423, 1404, 1349, 1308, 1226, 1174, 1088, 964, 887, 856, 775, 762, 738, 702, 682, 645, 616, 597; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (dd, *J* = 10.7, 4.4 Hz, 1H), 4.00 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.22 (dd, *J* = 11.2, 9.8 Hz, 1H), 5.64 (s, 2H), 6.85 (d, *J* = 6.4 Hz, 2H), 7.13−7.22 (m, 3H), 7.98 (d, *J* = 9.3 Hz, 2H), 8.33 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.7, 57.5, 66.6, 117.2, 124.8, 126.6, 127.8, 128.9, 129.0, 141.3, 141.5, 151.0, 154.2; HRMS (ESI) calcd for $C_{17}H_{14}N_4O_4S$ $(M + H)^+$ 371.0814, found 371.0815.

For (*R*)-**3g** $[\alpha]^{25}_D$ = +10.8 (*c* 0.425, $CHCl_3$); er >99:1, enantiomeric ratio was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isoproanol 90:10, flow rate = 1.0 mL/min; t_R = 66.75 min.

2-Amino-4-(4-chlorophenyl)-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3h). The general method described above was followed when **1h** (100 mg, 0.295 mmol) was reacted with malononitrile (28 μL, 0.443 mmol) in the presence of *t*-BuOK (50 mg, 0.443 mmol) using 20 mol % of $Sc(OTf)_3$ (29 mg, 0.059 mmol) at 60 °C for 5 min to afford **3h** (102 mg, 0.252 mmol) as a yellow solid in 85% yield; color changes to brown at 152 °C; R_f 0.37 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3424, 3327, 3216, 2922, 2192, 1662, 1606, 1534, 1490, 1468, 1429, 1402, 1365, 1346, 1313, 1277, 1163, 1086, 1052, 1012, 853, 819, 783, 753, 739, 680, 654, 615, 580; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.99 (dd, *J* = 9.8, 4.9 Hz, 1H), 4.17 (dd, *J* = 10.3, 10.5 Hz, 1H), 5.65 (s, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 8.39 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.2, 57.2, 66.2, 117.0, 124.9, 128.1, 129.1, 129.3, 133.9, 139.6, 141.4, 151.0, 154.3; HRMS (ESI) calcd for $C_{17}H_{13}ClN_4O_4S$, $(M + H)^+$ 405.0424, found 405.0421.

2-Amino-4-(3-chlorophenyl)-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3i). The general method described above was followed when **1i** (100 mg, 0.295 mmol) was reacted with malononitrile (28 μL, 0.443 mmol) in the presence of *t*-BuOK (50 mg, 0.443 mmol) using 20 mol % of $Sc(OTf)_3$ (29 mg, 0.059 mmol) at 60 °C for 5 min to afford **3i** (106 mg, 0.262 mmol) as a yellow solid in 89% yield; color changes to brown at 192 °C; R_f 0.31 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3423, 3329, 3271, 3221, 2190, 1662, 1603, 1530, 1474, 1434, 1403, 1368, 1349, 1316, 1278, 1168, 1088, 1052, 1003, 854, 786, 755, 742, 681, 655, 622, 599, 573; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.97 (m, 1H), 4.25 (dd, *J* = 11.0, 10.2 Hz, 1H), 5.64 (s, 2H), 6.59 (s, 1H), 6.83 (d, *J* = 7.3 Hz, 1H), 7.11−7.18 (m, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 8.38 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$+DMSO-d_6) δ 42.1, 56.7, 63.4, 117.6, 124.6, 125.2, 126.1, 127.4, 128.8, 130.1, 134.2, 141.1, 144.3, 150.6, 154.5; HRMS (ESI) calcd for $C_{17}H_{13}ClN_4O_4S$ $(M + H)^+$ 405.0424, found 405.0423.

2-Amino-4-(4-bromophenyl)-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3j). The general method described above was followed when **1j** (100 mg, 0.261 mmol) was reacted with malononitrile (25 μL, 0.391 mmol) in the presence of *t*-BuOK (44 mg, 0.391 mmol) using 20 mol % of $Sc(OTf)_3$ (26 mg, 0.052 mmol) at 60 °C for 5 min to afford **3j** (100 mg, 0.222 mmol) as a yellow solid in 85% yield; starts blackening at 150 °C; R_f 0.31 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3424, 3327, 3267, 3216, 3097, 2924, 2854, 2192, 1663, 1606, 1532, 1487, 1467, 1429, 1402, 1365, 1345, 1313, 1291, 12276, 1176, 1163, 1109, 1085, 1051, 1008, 972, 853, 816, 777, 752, 739, 680, 654, 621, 610, 579, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.98 (dd, *J* = 9.8, 4.9 Hz, 1H), 4.17 (dd, *J* = 10.8, 10.0 Hz, 1H), 5.64 (s, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 8.39 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.2, 57.1, 66.1, 117.0, 121.9, 124.9, 128.4, 129.0, 132.2, 140.2, 141.4, 151.0, 154.4; HRMS (ESI) calcd for $C_{17}H_{13}BrN_4O_4S$, $(M - H)^-$ 446.9763, found 446.9769.

2-Amino-4-(4-fluorophenyl)-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3k). The general method described above was followed when **1k** (100 mg, 0.310 mmol) was reacted with malononitrile (29 μL, 0.465 mmol) in the presence of *t*-BuOK (52 mg, 0.465 mmol) using 20 mol % of $Sc(OTf)_3$ (31 mg, 0.062 mmol) at 60 °C for 5 min to afford **3k** (105 mg, 0.271 mmol) as a yellow solid in 87% yield; melts to black liquid at 200 °C; R_f 0.30 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3442, 3321, 3264, 3209, 2195, 1660, 1606, 1532, 1508, 1468, 1433, 1403, 1361, 1349, 1317, 1277, 1226, 1164, 1086, 1052, 1012, 857, 837, 761, 737, 681, 618, 580; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.01 (dd, *J* = 9.8, 5.1 Hz, 1H), 4.16 (dd, *J* = 10.5, 10.2 Hz, 1H), 5.61 (s, 2H), 6.89 (d, *J* = 6.6 Hz, 4H), 8.03 (d, *J* = 8.8 Hz, 2H), 8.40 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.1, 57.3, 66.7, 116.0, 116.1, 124.9, 128.3, 128.4, 129.1, 136.8(2C), 141.4, 151.0, 154.2, 161.3, 163.3, ; HRMS (ESI) calcd for $C_{17}H_{13}FN_4O_4S$, $(M + H)^+$ 389.0720, found 389.0726.

2-Amino-1-(4-nitrophenylsulfonyl)-4-*p*-tolyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3l). The general method described above was followed when **1l** (100 mg, 0.314 mmol) was reacted with malononitrile (30 μL, 0.471 mmol) in the presence of *t*-BuOK (53 mg, 0.471 mmol) using 20 mol % of $Sc(OTf)_3$ (31 mg, 0.063 mmol) at 60 °C for 5 min to afford **3l** (107 mg, 0.278 mmol) as a yellow solid in 89% yield; starts blackening at 154 °C; R_f 0.37 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3426, 3329, 3271, 3220, 2924, 2191, 1665, 1606, 1529, 1470, 1429, 1367, 1347, 1314, 1281, 1177, 1088, 1054, 1007, 851, 809, 757, 740, 681, 619, 555 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.59 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.96 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.20 (dd, *J* = 10.5, 10.3 Hz, 1H), 5.59 (s, 2H), 6.72 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 8.32 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 42.3, 57.7, 66.8, 117.3, 124.8, 126.4, 129.0, 129.7, 137.7, 138.3, 141.5, 150.9, 154.1; HRMS (ESI) calcd for $C_{18}H_{16}N_4O_4S$, $(M + H)^+$ 385.0971, found 385.0974.

2-Amino-4-(4-*tert*-butylphenyl)-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3m). The general method described above was followed when **1m** (100 mg, 0.277 mmol) was reacted with malononitrile (26 μL, 0.416 mmol) in the presence of *t*-

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BuOK (47 mg, 0.416 mmol) using 20 mol % of $Sc(OTf)_3$ (27 mg, 0.055 mmol) at 60 °C for 5 min to afford **3m** (99 mg, 0.232 mmol) as a yellow solid in 84% yield; color changes to black at 124 °C; R_f 0.40 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3436, 3325, 3265, 3211, 2962, 2926, 2869, 2193, 1664, 1605, 1531, 1464, 1430, 1402, 1366, 1348, 1315, 1271, 1166, 1087, 1050, 1013, 855, 833, 784, 754, 740, 681, 617, 587; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 3.59 (dd, J = 10.8, 4.6 Hz, 1H), 3.99 (dd, J = 9.8, 4.6 Hz, 1H), 4.19 (dd, J = 10.7, 10.0 Hz, 1H), 5.58 (s, 2H), 6.76 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 34.5, 42.2, 57.5, 66.9, 117.3, 124.8, 125.9, 126.2, 129.1, 138.0, 141.5, 150.9(2C), 154.1; HRMS (ESI) calcd for $C_{21}H_{22}N_4O_4S$, $(M + H)^+$ 427.1440, found 427.1455.

2-Amino-4-(4-hydroxyphenyl)-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3n). The general method described above was followed when **1n** (100 mg, 0.276 mmol) was reacted with malononitrile (26 μL, 0.414 mmol) in the presence of *t*-BuOK (47 mg, 0.414 mmol) using 20 mol % of $Sc(OTf)_3$ (27 mg, 0.055 mmol) at 60 °C for 5 min to afford **3n** (94 mg, 0.243 mmol) as a yellow solid in 88% yield; blackens at 208 °C; R_f 0.31 (55% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3462, 3424, 3361, 3222, 3109, 2190, 1651, 1609, 1529, 1468, 1426, 1364, 1315, 1268, 1169, 1140, 1085, 1049, 1008, 855, 826, 760, 738, 681, 653; ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6) δ 2.59−2.60 (m, 1H), 3.53 (dd, J = 11.0, 4.9 Hz, 1H), 3.90 (dd, J = 9.8, 4.6 Hz, 1H), 4.15 (dd, J = 10.7, 9.8 Hz, 1H), 6.42 (s, 2H), 6.60 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 8.35 (d, J = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.9, 57.6, 65.3, 115.6, 118.0, 124.6, 127.5, 129.0, 132.1, 141.5, 150.6, 154.1, 156.7; HRMS (ESI) calcd for $C_{17}H_{14}N_4O_5S$, $(M + H)^+$ 387.0763, found 387.0760.

(*S*)-2-Amino-4-benzyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3o). The general method described above was followed when **1o** (100 mg, 0.348 mmol) was reacted with malononitrile (33 μL, 0.522 mmol) in the presence of *t*-BuOK (59 mg, 0.522 mmol) using 20 mol % of $Sc(OTf)_3$ (34 mg, 0.069 mmol) at 60 °C for 30 min to afford **3o** (117 mg, 0.331 mmol) as a white solid in 95% yield; mp 141−143 °C; R_f 0.46 (25% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +156.9 (*c* 0.385, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3454, 3364, 2924, 2854, 2190, 1730, 1648, 1595, 1495, 1454, 1425, 1359, 1294, 1266, 1165, 1089, 1034, 1004, 814, 738, 703, 664, 590, 548, 531; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20−2.31 (m, 2H), 2.45 (s, 3H), 2.89 (dd, J = 13.5, 9.8 Hz, 1H), 3.24 (dd, J = 13.5, 3.7 Hz, 1H), 4.11−4.16 (m, 1H), 5.40 (s, 2H), 7.22−7.26 (m, 3H), 7.30−7.33 (m, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 30.1, 42.6, 59.9, 62.6, 118.4, 127.1, 127.3, 128.7, 129.7, 130.4, 134.3, 136.2, 145.4, 154.1; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_2S$ $(M + H)^+$ 354.1276, found 354.1275.

(*S*)-2-Amino-5-methyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3p). The general method described above was followed when **1p** (100 mg, 0.473 mmol) was reacted with malononitrile (45 μL, 0.709 mmol) in the presence of *t*-BuOK (80 mg, 0.709 mmol) using 20 mol % of $Sc(OTf)_3$ (47 mg, 0.095 mmol) at 60 °C for 30 min to afford **3p** (121 mg, 0.436 mmol) as a white solid in 95% yield; mp 146−148 °C; R_f 0.46 (25% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +73.4 (*c* 0.515, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3443, 3346, 2963, 2926, 2182, 1920, 1643, 1595, 1494, 1420, 1378, 1357, 1339, 1311, 1294, 1210, 1159, 1091, 1029, 890, 829, 813, 701, 680, 663, 626, 588; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, J = 6.8 Hz, 3H), 2.06 (dd, J = 13.2, 3.4 Hz, 1H), 2.46 (s, 3H), 2.58 (dd, J = 13.2, 9.8 Hz, 1H), 3.98−4.06 (m, 1H), 5.48 (s, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 23.6, 33.4, 57.9, 59.3, 118.7, 127.3, 130.3, 134.2, 145.3, 154.0; HRMS (ESI) calcd for $C_{13}H_{15}N_3O_2S$, $(M + H)^+$ 278.0963, found 278.0967.

(4*S*,5*S*)-2-Amino-4-phenyl-5-propyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3q). The general method described above was followed when **1q** (100 mg, 0.317 mmol) was reacted with malononitrile (30 μL, 0.476 mmol) in the presence of *t*-BuOK (53 mg, 0.476 mmol) using 20 mol % of $Sc(OTf)_3$ (31 mg, 0.063 mmol) at 60 °C for 2.5 h to afford **3q** (121 mg, 0.315 mmol) as a white solid in >99% yield as a single diastereomer; mp 140−142 °C; R_f 0.46 (25% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +52.8 (*c* 0.378, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3452, 3320, 3211, 2963, 2938, 2877, 2200, 1642, 1597, 1493, 1454, 1420, 1357, 1273, 1189, 1165, 1087, 1026, 993, 943, 884, 848, 809, 754, 728, 705, 662, 582; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (t, J = 7.3 Hz, 3H), 0.99−1.05 (m, 2H), 1.24−1.27 (m, 1H), 1.45−1.55 (m, 1H), 2.49 (s, 3H), 3.89 (d, J = 8.6 Hz, 1H), 4.04−4.12 (m, 1H), 5.53 (s, 2H), 7.10 (d, J = 6.9 Hz, 2H), 7.23−7.30 (m, 3H), 7.41 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.9, 21.9, 33.5, 48.5, 66.4, 66.8, 118.1, 127.4, 127.9, 128.6, 128.9, 130.5, 134.4, 136.0, 145.5, 155.7; HRMS (ESI) calcd for $C_{21}H_{23}N_3O_2S$ $(M + H)^+$ 382.1589, found 382.1591.

(4*S*,5*S*)-5-Allyl-2-amino-4-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3r). The general method described above was followed when **1r** (100 mg, 0.319 mmol) was reacted with malononitrile (30 μL, 0.479 mmol) in the presence of *t*-BuOK (54 mg, 0.479 mmol) using 20 mol % of $Sc(OTf)_3$ (31 mg, 0.064 mmol) at 60 °C for 2.0 h to afford **3r** (121 mg, 0.318 mmol) as a white solid in >99% yield as a single diastereomer; mp 160−162 °C; R_f 0.45 (25% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +113.1 (*c* 0.175, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3445, 3316, 2924, 2854, 2191, 1729, 1640, 1596, 1453, 1421, 1356, 1274, 1165, 1087, 1032, 995, 914, 889, 809, 749, 706, 667, 569; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94−1.98 (m, 1H), 2.28−2.34 (m, 1H), 2.49 (s, 3H), 3.98 (d, J = 8.9 Hz, 1H), 4.13 (q, J = 6.7 Hz, 1H), 4.81 (d, J = 17.1 Hz, 1H), 4.90 (d, J = 10.1 Hz, 1H), 5.36−5.42 (m, 1H), 5.59 (s, 2H), 7.12 (d, J = 6.7 Hz, 2H), 7.25−7.30 (m, 3H), 7.41 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 36.1, 48.1, 66.0, 66.1, 117.9, 118.0, 127.4, 128.0, 128.6, 129.1, 130.5, 133.3, 134.4, 135.8, 145.6, 155.6; HRMS (ESI) calcd for $C_{21}H_{21}N_3O_2S$, $(M + H)^+$ 380.1433, found 380.1430.

2-Amino-5-((*tert*-butyldimethylsilyloxy)methyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (3s). The general method described above was followed when **1s** (100 mg, 0.239 mmol) was reacted with malononitrile (23 μL, 0.359 mmol) in the presence of *t*-BuOK (40 mg, 0.359 mmol) using 20 mol % of $Sc(OTf)_3$ (24 mg, 0.048 mmol) at 60 °C for 2.0 h to afford **3s** (115 mg, 0.238 mmol) as a white solid in >99% yield as a single diastereomer; mp 166−168 °C; R_f 0.41 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3450, 3304, 3259, 3208, 2951, 2928, 2855, 2194, 1653, 1595, 1495, 1458, 1423, 1354, 1307, 1255, 1188, 1162, 1143, 1090, 1064, 1031, 1006, 912, 890, 839, 813, 780, 756, 704, 666, 600, 567; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 3H), −0.12 (s, 3H), 0.80 (s, 9H), 2.50 (s, 3H), 3.47−3.54 (m, 2H), 3.98−4.03 (m, 1H), 4.07 (d, J = 9.8 Hz, 1H), 5.56 (s, 2H), 7.19 (d, J = 6.6 Hz, 2H), 7.23−7.28 (m, 3H), 7.41 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.7, −5.6, 18.2, 21.8, 25.9, 47.1, 62.3, 66.3, 66.4, 118.0, 127.4, 127.7, 128.2, 129.4, 130.5, 134.2, 135.7, 145.5, 155.8; HRMS (ESI) calcd for $C_{25}H_{33}N_3O_3SSi$, $(M + H)^+$ 484.2090, found 484.2094.

Procedure for Denosylation of Compound 3g. Compound **3g** (100 mg, 0.269 mmol) dissolved in CH_3CN (4.0 mL) was added to a suspension of K_2CO_3 (149 mg, 1.076 mmol, 4.0 equiv) in CH_3CN (4.7 mL), followed by addition of PhSH (83.0 μL, 0.809 mmol, 3.0 equiv) at room temperature under nitrogen atmosphere. Next DMSO (0.3 mL) was added to the reaction mixture, and stirring was continued at room temperature for 1 h. After complete consumption of the starting compound (monitored by TLC using 20% ethyl acetate in petroleum ether as the eluent), the reaction mixture was evaporated to give a pale yellow residue. The crude compound (the pale yellow residue) was purified by acid−base treatment as described below.

Acid−Base Treatment. To the pale yellow residue were added water (5.0 mL) and diethyl ether (10.0 mL). After separating, the organic layer was washed with dilute $NaHCO_3$ solution (3 × 2.0 mL). The organic layer was acidified with 5% HCl (5.0 mL). The aqueous layer was separated, and the organic layer was extracted with 5% HCl (2 × 5.0 mL). The combined aqueous extract was covered with a layer of diethyl ether (10.0 mL) and was made alkaline with aqueous 5 N NaOH solution (pH approximately 10) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 10.0 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to provide **4** in 80% yield (40 mg, 0.216 mmol) as a white solid in pure form as indicated by ^{1}H and ^{13}C NMR and HRMS. Compound **4** was found to decompose

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slowly at room temperature and upon exposure to light and/or air. However, it can be stored under Ar at lower temperature (−20 °C).

2-Amino-4-phenyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (4). R_f 0.35 (10% methanol in chloroform); IR ν_{max} (KBr, cm^{-1}) 3418, 3342, 3373, 3258, 3222, 2922, 2887, 2156, 1654, 1639, 1591, 1509, 1468, 1450, 1343, 1312, 1204, 1155, 1071, 1028, 705, 767, 594, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57−3.68 (m, 1H), 3.68−3.76 (m, 1H), 3.77−3.87 (m, 1H), 4.02−4.13 (m, 1H), 4.42−5.10 (m, 2H) 7.19−7.30 (m, 5H); ^{1}H NMR (500 MHz, $CDCl_3$ + D_2O) δ 3.72 (dd, J = 13.7, 8.3 Hz, 1H), 3.88 (t, J = 8.0 Hz, 1H), 4.15 (dd, J = 13.8, 8.1 Hz, 1H), 4.71 (s, 1H), 7.23−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.7, 50.9, 62.4, 116.4, 127.0, 128.0, 128.8, 129.2, 158.0; HRMS (ESI) calcd for $C_{11}H_{11}N_3$, $(M + H)^+$ 186.1031, found 186.1031.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for all the new compounds and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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