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Note

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Modified Asymmetric Strecker Reaction of Aldehyde with Secondary amine: A Protocol for the Synthesis of *S*-Clopidogrel (an Antiplatelet agent)

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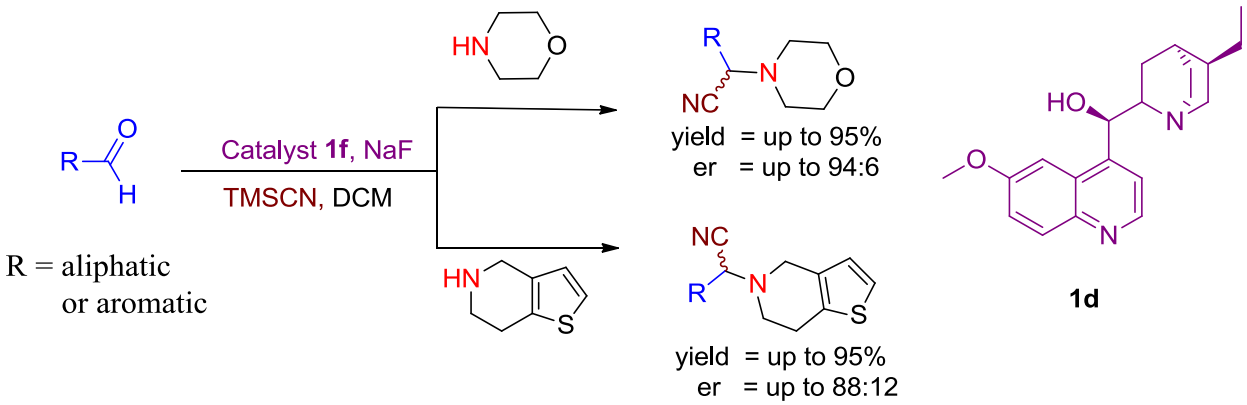
ABSTRACT:



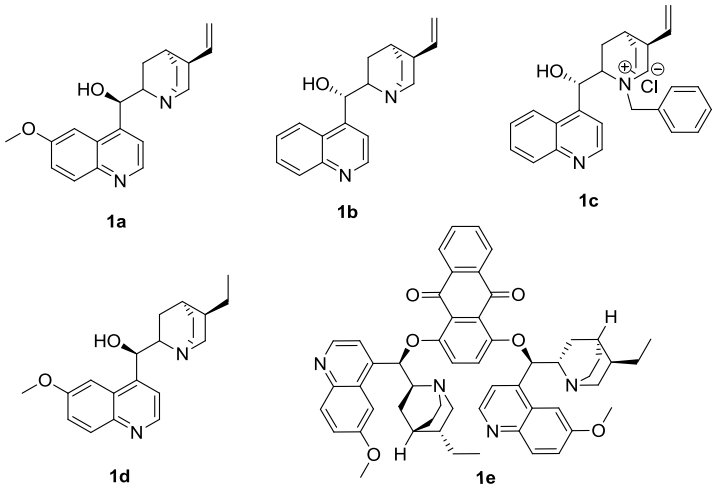
A first approach for catalytic asymmetric Strecker reaction of aldehydes with secondary amine in the presence of sodium fluoride using hydroquinine as chiral catalyst was developed. The catalytic system gave α-aminonitriles in excellent yields (up to 95%) and high enantioselectivities (er up to 94:6). The efficacy of the chiral product was successfully fulfilled in the improved synthesis of (*S*)-clopidogrel (an antiplatelet agent).

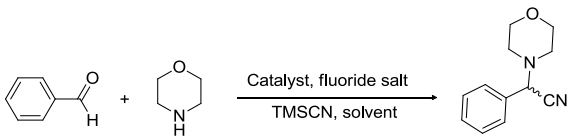
α-Aminonitriles[1] are useful intermediates for the synthesis of pharmaceutically important chiral amino acids[2] and their derivatives, ligands, peptides and natural products.[3] The enantioselective addition of cyanide to imines (Strecker type reaction) to synthesize α-aminonitriles is well

documented and are often catalyzed by enzymes,[1b] organo-catalyst[4] and metal complexes.[5] Yet, the enantioselective addition of cyanide to iminium salt (in situ generated by the reaction of an aldehyde with secondary amine) to synthesize α-aminonitrile derivatives is not reported, though few reports are available in the literature[6] for its racemic version. Harwood et al. have reported diastereoselectve Strecker reaction of chiral iminium ion derived from (*S*)-5-phenylmorpholin-2-one.[7] In this reaction dry HCl was used as catalyst with CuCN as cyanide source which gave the product with diastereomeric ratio (up to 15.4:1) which was most likely substrate driven. Herein, we are reporting for the first time the synthesis of asymmetric α-aminonitriles by asymmetric Strecker reaction of various iminium ions by using several chiral alkaloids as organocatalyst **1a-1e** in the presence of sodium fluoride. These iminium ions were generated in situ by the reaction of various aldehydes with secondary amines viz., morpholine **2** and 4,5,6,7-tetrahydrothieno[3,2-c]pyridine **3**. The Strecker reaction with secondary amine **3** was studied for their use as precursor to the drug clopidogrel. The choice of chiral alkaloids was based on their known prowess in catalyzing asymmetric Strecker reaction.[8] When we conducted the model reaction with benzaldehyde and morpholine in the presence of quinine **1a** (30 mol%) using TMSCN as a cyanide source in CH_2Cl_2 as solvent at -20 ^oC for 16 h the product formed was in trace quantity (Table 1, entry 1). On the addition of sodium fluoride (10 mol%) to the above reaction, there was sizeable improvement in the product yield (89%) and enantioselectivity (er, 73:27) (entry 2) under the same reaction condition. The consideration of NaF as an additive was based on strong affinity of fluoride ion towards the silicon which was envisaged to facilitate the polarization of Si-CN bond of TMSCN. In fact, when the above model reaction was conducted in the absence of quinine, but in the presence of NaF, the product (racemic) formed in good yield (entry 3). Next, we screened other related alkaloids **1b**-**1e** for their catalytic ability towards the above model Strecker reaction keeping other reaction parameters constant (entries 4-7). Among these alkaloids, **1d** was found to be better catalyst in terms of enantioselectivity (entry 6). A slow and simultaneous addition of NaF and TMSCN (over a period of 3 h) to a stirred solution of benzaldehyde and morpholine in the presence of **1d** in CH_2Cl_2 at -20 ^oC significantly improved the enantioselectivity of the product (entry 8) possibly by suppressing the background reaction (responsible for the racemic product) caused by NaF. The same reaction when conducted at further reduced temperature (-40 ^oC) gave the product in lower yield but with no improvement in the enantioselectivity (entry 9). Hence, -20 ^oC was taken as preferred temperature to see the

effect of solvent on this reaction (entries 10-12), however none of these (toluene, THF and CH_3CN) could match the performance of CH_2Cl_2 (entry 8). There is a possibility that source of fluoride may influence the performance of Strecker reaction hence, the effect of various fluoride salts e.g., LiF, NaF, KF, NH_4F and $(t\text{-}Bu)_4NF$ was evaluated under the above optimized condition (entries 13-16) where NaF was found to be most effective.

Table 1. Screening of the catalysts for the catalytic modified asymmetric Strecker reaction[a] with secondary amine





entry	catalyst	solvent	fluoride salt	yield (%)[b]	er[c]
1	**1a**	dichloromethane	-	trace	Nd
2	**1a**	dichloromethane	NaF	89	73:27
3	**-**	dichloromethane	NaF	82	-
4	**1b**	dichloromethane	NaF	82	66:34
5	**1c**	dichloromethane	NaF	85	70:30
6	**1d**	dichloromethane	NaF	90	82:18

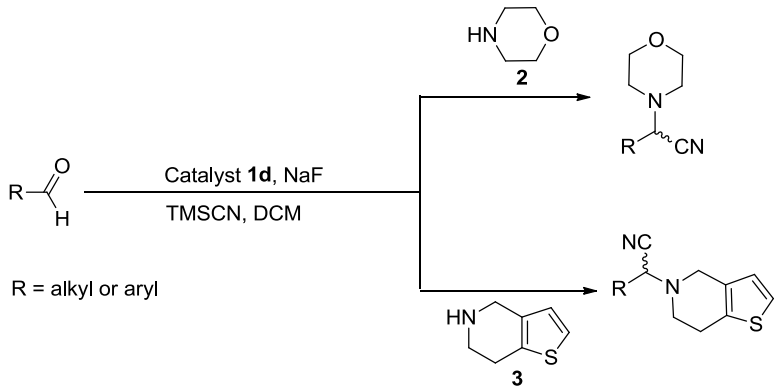
7	**1e**	dichloromethane	NaF	80	54:46
8	**1d**[d]	dichloromethane	NaF	90	94:6
9	**1d**[e]	dichloromethane	NaF	78	94:6
10	**1d**	toluene	NaF	76	86:14
11	**1d**	tetrahydrofuran	NaF	88	89:11
12	**1d**	acetonitrile	NaF	85	80:20
13	**1d**	dichloromethane	LiF	80	80:20
14	**1d**	dichloromethane	KF	92	70:30
15	**1d**	dichloromethane	NH_4F	85	75:25
16	**1d**	dichloromethane	TBAF	92	88:12

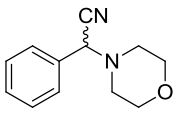
[a]Reagents and conditions: benzaldehyde (0.032 g, 0.3 mmol), morpholine (0.028 g, 0.32 mmol), catalyst (30 mol%), NaF (10 mol%), dichloromethane (0.8 mL) were taken and TMSCN (1.2 equiv.) was added over 3 h at -20 ^{o}C (total reaction time 16 h). [b]Isolated yield. [c]Determined by HPLC analysis on chiral OD column. [d]Solid NaF and TMSCN were simultaneously added slowly over 3 h. [e]Reaction was carried out at -40 ^{o}C.

The scope of the present Strecker protocol was extended to various substituted benzaldehydes, naphthaldehyde, cyclohexylcarboxaldehyde and isovaleraldehyde with secondary amines **2** and **3** under the optimized condition (as entry 8 of Table 1) and the results are summarized in Scheme 1. The outcomes of these reactions however, do not suggest a trend indicating the effect of electronic and steric properties of the substrates used herein. Among the various substrates used, 2-Cl-benzaldehyde with secondary amine **3** was of particular interest as its product gave antiplatelet agent (*S*)-clopidogrel[9] (er 78:22) in two steps[10] (Scheme 2) against multistep synthesis reported in the literature.[9] It is worth mentioning here that the above optimized protocol for the modified Strecker reaction of benzaldehyde with morpholine catalysed by several organocatalysts like L-proline, L-Boc-phenylalanine, (*S*)-mandelic acid, L-

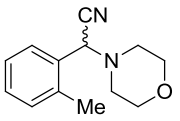
diethyltartarate, (*S*)-BINOL, and tosylated (*1S,2S*)-1,2-diaminocyclohexane gave racemic product or with poor enantiomeric ratio (data are given in supporting information Table- 1S).

Scheme 1. Scope of the catalytic modified asymmetric Strecker reaction with secondary amine

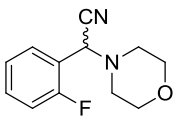




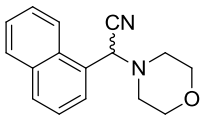
4a, yield = 90%, er = 94:6



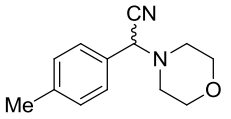
4b, yield = 92%, er = 92:8



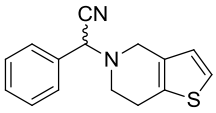
4c, yield = 95%, er = 92:8



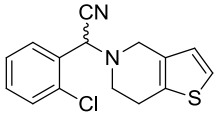
4d, yield = 90%, er = 91.5:8.5



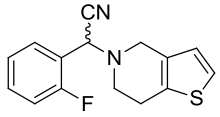
4e, yield = 90%, er = 79.5:20.5



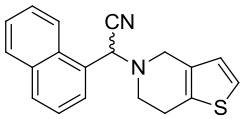
4f, yield = 95%, er = 81:19



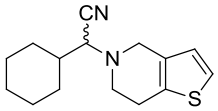
4g, yield = 92%, er = 78:22



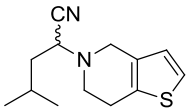
4h, yield = 92%, er = 81.5:18.5



4i, yield = 93%, er = 80:20

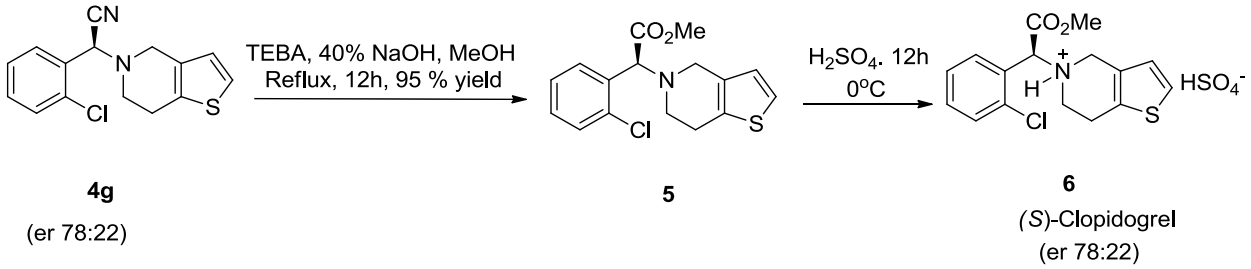


4j, yield = 94%, er = 88:12



4k, yield = 91%, er = 65:35

Scheme 2. Synthetic utility of the product: synthesis of (*S*)-Clopidogrel

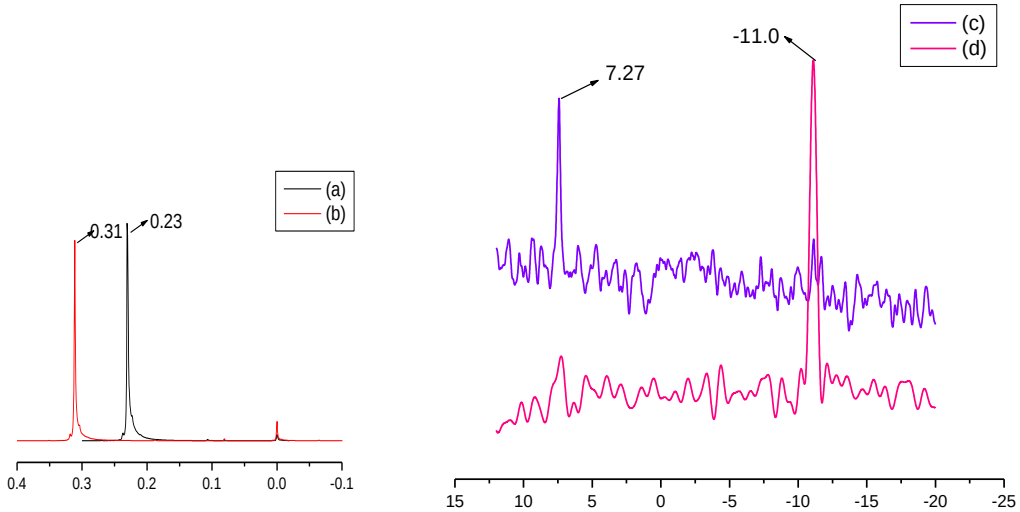


4g
(er 78:22)

5

6
(*S*)-Clopidogrel
(er 78:22)

In order to demonstrate the suggested influence of fluoride on TMSCN ^{1}H, ^{13}C and ^{29}Si NMR spectra of TMSCN in the presence of NaF were recorded in $CDCl_3$ (Figure 1). All three methyl group of TMSCN (spectrum a) that appeared as a singlet at 0.23 ppm in ^{1}H NMR got downfield shifted by 40.5 Hz on the addition of NaF (0.31 ppm, spectrum b). This phenomenon was also seen in ^{13}C NMR where methyl carbon signal of TMSCN at -1.25 ppm was downfield shifted (8 Hz) to -1.23 ppm on the addition of NaF. However, more conclusive evidence was seen in ^{29}Si NMR, where a clear downfield shifting of Si signal of TMSCN from -11.10 ppm to 7.42 ppm was observed on the addition of NaF (Figure 1). This shift also suggests that there is no replacement of NC^- of TMSCN with F^-, as in the event of this the ^{29}Si signal of $(CH_3)_3SiF$ would have appeared at 30 ppm.[11] Consequently, it can be suggested that NaF is merely assisting in polarising the Si-CN bond in order to facilitate the transfer of CN to the substrate iminium ion.



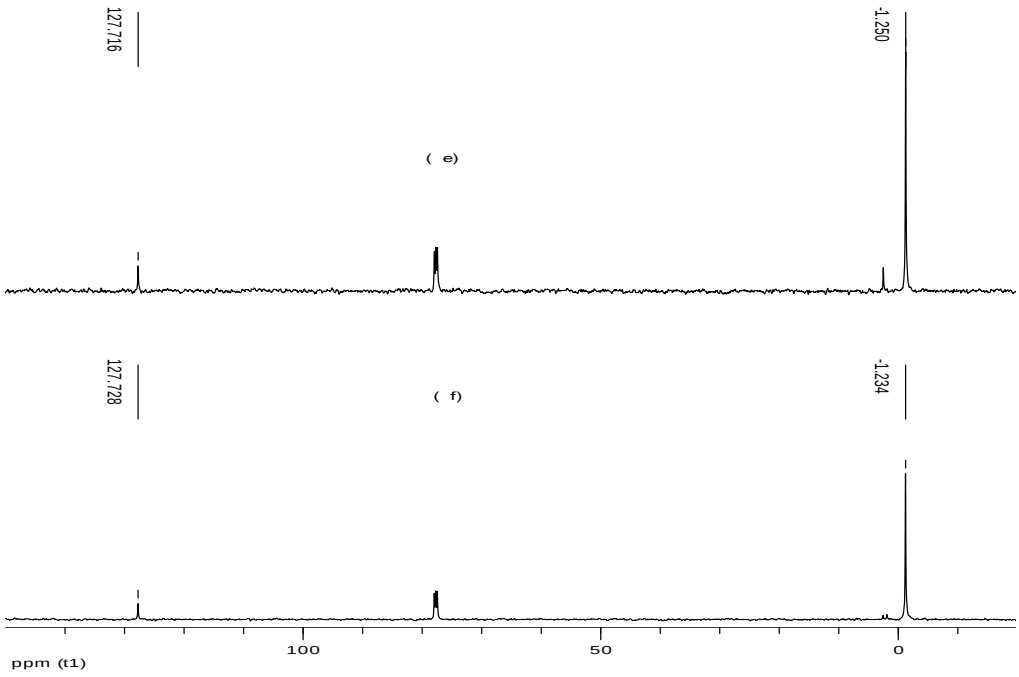


Figure 1. NMR comparison (a) ^{1}H NMR of TMSCN; (b) TMSCN + NaF; (c) ^{29}Si NMR of TMSCN + NaF; (d) ^{29}Si NMR of TMSCN; (e) ^{13}C NMR of TMSCN and (f) ^{13}C NMR of TMSCN+ NaF.

In conclusion, we have developed a straightforward catalytic protocol for the asymmetric modified Strecker reaction of aldehydes with secondary amine to synthesize α–aminonitriles with enantiomeric ratios (er) of up to 94:6. The present protocol also provides a new route for the synthesis of *S*-Clopidogrel- an antiplatelet agent.[12]

EXPERIMENTAL SECTION

Typical procedure for asymmetric Strecker reaction of aldehyde with secondary amine using benzaldehyde and morpholine as an example:

Caution! *TMSCN must be used carefully in well-ventilated hood due to its high toxicity*. A mixture of benzaldehyde (0.032 g, 0.3 mmol), morpholine (0.028 g, 0.32 mmol) and catalyst **1d** (0.09 mmol) in CH_2Cl_2 (0.8 mL) was cooled to -20 ^{0}C, to which TMSCN (0.36 mmol) NaF (0.03 mmol) were added simultaneously over 3.5 h and the reaction mixture was allowed to stir for 16 h. After the reaction was completed, the reaction mass was filtered by passing through a pad of celite and washed with water (3 x 15 mL) followed by brine and the organic layer was separated

and dried with anhydrous Na_2SO_4. The solution was filtered, evaporated under reduced pressure at ambient temperature and the α-aminonitrile product was purified by flash column chromatography on silica gel (eluted with hexane: ethylacetate = 90:10). The enantiomeric ratio of α-aminonitrile was determined by HPLC analysis.

2-Morpholino-2-phenyl acetonitrile (4a).

55 mg, 90% yield, white solid (amorphous); mp 70-72 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (t, *J* = 5.0 Hz, 1H), 7.43-7.37 (m, 3H), 4.82 (s, 1H), 3.77-3.70 (m, 4H), 2.59 (t, *J* = 4.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 132.1, 129.3, 129.0, 128.2, 115.4, 66.9, 62.6, 50.2; $[\alpha]_D^{30}$ = -28.2 (*c* = 0.035 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{12}H_{14}N_2O$ (M+1) 203.11, Found 203.12; Anal. Calcd. For $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85, O, 7.91. Found: C, 71.28; H, 6.95; N, 13.83, O, 7.90; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 254 nm): t (major) = 9.94 min, t (minor) = 10.79 min, er = 94:6.

2-Morpholino-2-(*o*-tolyl) acetonitrile (4b).

59 mg, 92% yield, viscous liquid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* =10.0 Hz, 1H), 7.38-7.36 (m, 1H), 7.34-7.29 (m, 2H), 4.93 (s, 1H), 3.77-3.72 (m, 4H), 2.66-2.63 (m, 4H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 137.4, 131.2, 130.5, 129.2, 128.7, 125.9, 115.3, 66.7, 60.6, 49.7, 18.8; $[\alpha]_D^{30}$ = -23.5 (*c* = 0.031 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{13}H_{16}N_2O$ (M+1) 217.13, Found 217.11; Anal. Calcd. For $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95, O, 7.40. Found: C, 72.18; H, 7.45; N, 12.96, O, 7.41;. HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.6 mL/ min, λ = 254 nm): t (major) = 19.78 min, t (minor) = 22.58 min, er = 92:8.

2-(2-Fluorophenyl)-2-morpholino acetonitrile (4c).

62 mg, 95% yield, viscous liquid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.55-7.52 (m,1H), 7.43-7.39 (m, 1H), 7.22 (t, *J* = 10.5 Hz, 1H), 7.15 (t, *J* = 10.5 Hz, 1H), 5.03 (s, 1H), 3.72-3.68 (m, 4H), 2.62-2.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 161.5, 159.5, 131.3, 130.2, 124.2, 119.9, 119.8, 116.2, 116.1, 114.8, 66.5, 56.2, 49.9; $[\alpha]_D^{30}$ = -31.1 (*c* = 0.032 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{12}H_{13}FN_2O$ (M+1) 221.10, Found: 221.11; Anal. Calcd. For $C_{12}H_{13}FN_2O$: C, 65.44; H, 5.95; N, 12.72, O, 7.26. Found: C, 65.43; H, 5.96; N, 12.70, O, 7.25;

HPLC (CHIRALPAK AD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 247 nm): t (major) = 17.88 min, t (minor) = 19.20 min, er = 92:8.

2-Morpholino-(2-naphthalen-1-yl) acetonitrile (4d).

68 mg, 90% yield, white solid (amorphous); mp 128-130 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (t, *J* = 5.5 Hz, 1H), 7.91-7.86 (m, 2H), 7.52-7.49 (m, 2H), 7.05 (d, *J* = 5.0 Hz, 1H), 6.67 (d, *J* = 5.0 Hz, 1H), 5.66 (s, 1H), 3.83 (d, *J* = 14.0 Hz, 1H), 3.66 (d, *J* = 10.5 Hz, 1H), 2.99 (t, *J* = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 135.5, 132.4, 131.8, 130.3, 129.1, 128.6, 128.2, 127.8, 126.2, 125.1, 116.6, 68.1, 62.5, 51.3; $[\alpha]_D^{30}$ = -41.0 (*c* = 0.032 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{16}H_{16}N_2O$ 252.13, Found: 252.11; Anal. Calcd. For $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10, O, 6.34. Found: C, 76.18; H, 6.41; N, 11.09, O, 6.33; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 247 nm): t (major) = 9.99 min, t (minor) = 8.96 min, er = 91.5:8.5.

2-Morpholino-2-(*p*-tolyl) acetonitrile (4e).

58 mg, 90% yield, white solid (amorphous); mp 91-93 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 10.0 Hz, 2H), 4.70 (s, 1H), 3.65-3.63 (m, 4H), 2.52-2.49 (m, 4H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 140.4, 130.9, 129.3, 116.8, 68.1, 63.6, 51.3, 22.5; $[\alpha]_D^{30}$ = +21.0 (*c* = 0.030 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{13}H_{16}N_2O$ (M+1) 217.13, Found: 217.12; Anal. Calcd. For $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95, O, 7.40. Found: C, 72.15; H, 7.44; N, 12.96, O, 7.43; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 254 nm): t (major) = 7.73 min, t (minor) = 7.23 min, er = 79.5:20.5.

2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-phenylacetonitrile (4f).

72 mg, 95% yield, white solid (amorphous); mp 84-86 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 9.0, Hz, 2H), 7.43-7.40 (m, 3H), 7.10 (d, *J* = 5.0 Hz, 1H), 6.71 (d, *J* = 5.0 Hz, 1H), 5.09 (s, 1H), 3.71 (d, *J* = 14.0Hz, 1H), 3.66 (d, *J* = 14.0, 1H), 2.97-2.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 133.4, 130.5, 130.3, 129.3, 126.5, 124.6, 116.9, 63.7, 51.3, 49.1, 27.1; $[\alpha]_D^{32}$ = + 33.4 (*c* = 0.030 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{15}H_{14}N_2S$ 254.09, Found 254.10; Anal. Calcd. For $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01, S, 12.61. Found: C, 70.85; H,

5.54; N, 11.00, S, 12.64; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 247 nm): t (major) = 16.88 min, t (minor) = 12.06 min, er = 81:19.

2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl) acetonitrile (4g).

79 mg, 92% yield, white solid (amorphous); mp 123-125 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66-7.61 (m, 1H), 7.39-7.29 (m, 3H), 6.62 (d, *J* = 12.5 Hz, 1H), 5.25 (s, 1H), 3.70 (d, *J* = 15.5 Hz, 1H), 3.55 (d, *J* = 15.5, 1H), 2.95-2.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 134.6, 133.0, 132.5, 130.9, 130.6, 130.1, 126.9, 125.1, 123.1, 115.2, 59.3, 49.5, 47.8, 25.6; $[\alpha]_D^{30}$ = +30.7 (*c* = 0.030 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{15}H_{13}ClN_2S$ (M+1) 289.05, Found: 289.00; Anal. Calcd. For $C_{15}H_{13}ClN_2S$: C, 62.38; H, 4.54; N, 9.70, S, 11.10. Found: C, 62.35; H, 4.56; N, 9.71, S, 11.13; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 247 nm): t (major) = 8.36 min, t (minor) = 7.76 min, er = 78:22.

2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(2-fluorophenyl) acetonitrile (4h).

75 mg, 92% yield, white solid (amorphous); mp 92-94 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (t, *J* = 7.5 Hz, 1H), 7.45-7.41 (m, 1H), 7.13 (t, *J* = 9.25 Hz, 1H), 7.09 (d, *J* = 5.5 Hz, 1H), 6.71 (d, *J* = 5.0 Hz, 1H), 5.28 (s, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.68 (d, *J* = 14.0 Hz, 1H), 3.02-2.96 (m, 3H), 2.91- 2.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 162.9, 160.9, 134.2, 133.9, 132.7, 131.5, 126.5, 125.6, 124.6, 117.5, 116.5, 57.3, 51.0, 49.3, 27.0; $[\alpha]_D^{30}$ = -27.4 (*c* = 0.030 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{15}H_{13}FN_2S$ (M+1) 289.05, Found 289.00; Anal. Calcd. For $C_{15}H_{13}FN_2S$: C, 66.15; H, 4.81; N, 10.29, S, 11.77. Found: C, 66.11; H, 4.80; N, 10.25, S, 11.75; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 247 nm): t (major) = 12.56 min, t (minor) = 11.65 min, er = 81.5:18.5.

2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(naphthalen-1-yl) acetonitrile (4i).

84 mg, 93% yield, white solid (amorphous); mp 68-70 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (t, *J* = 5.0 Hz, 1H), 7.92-7.87 (m, 3H), 7.54-7.50 (m, 3H), 7.07 (d, *J* = 5.0 Hz, 1H), 6.69 (d, *J* = 5.0 Hz, 1H), 5.67 (s, 1H), 3.85 (d, *J* = 14.0 Hz, 1H), 3.65 (d, *J* = 14.0 Hz, 1H), 3.00 (t, *J* = 5.5 Hz, 2H), 2.94-2.89 (m, 1H), 2.80-2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 135.5, 134.4, 134.1, 132.4, 131.7, 130.1, 129.7, 128.3, 127.7, 126.5, 126.2, 125.2, 124.5, 116.9, 62.1, 57.2, 48.9, 27.1; $[\alpha]_D^{32}$ = -32.4 (*c* = 0.035 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{19}H_{16}N_2S$

(M+1) 305.11, Found: 305.10; Anal. Calcd. For $C_{19}H_{16}N_2S$: C, 74.97; H, 5.30; N, 9.20, S, 10.53. Found: C, 74.94; H, 5.34; N, 9.18, S, 10.50; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.6 mL/ min, λ = 274 nm): t (major) = 8.50 min, t (minor) = 7.85 min, er = 80:20.

2-cyclohexyl-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl) acetonitrile (4j).

73 mg, 94% yield, yellowish white solid (amorphous); mp 80-82 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 5.0 Hz, 1H), 6.72 (d, *J* = 5.0 Hz, 1H), 3.72 (d, *J* = 10.0 Hz, 1H), 3.55 (d, *J* = 15.0, 1H), 3.32 (d, *J* = 10.0 Hz, 1H), 3.01-2.96 (m, 1H), 2.93-2.88 (m, 2H), 2.73-2.68 (m, 1H), 2.00 (t, *J* = 15.0, 2H), 1.81-1.78 (m, 2H), 1.72-1.68 (m, 3H), 1.32-1.15 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 135.1, 127.3, 125.3, 118.8, 52.1, 50.1, 40.1, 33.0, 32.0, 28.5, 27.8, 27.6; $[\alpha]_D^{30}$ = +30.5 (*c* = 0.038 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{15}H_{20}N_2S$ (M+1) 261.14, Found 261.10; Anal. Calcd. For $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76, S, 12.31. Found: C, 69.20; H, 7.71; N, 10.75, S, 12.34; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 254 nm): t (major) = 9.80 min, t (minor) = 8.88 min, er = 88:12.

2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-methylpentanenitrile (4k).

63 mg, 91% yield viscous liquid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 5.0 Hz, 1H), 6.74 (d, *J* = 5.5 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 3.75 (d, *J* = 7.5, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 3.04-2.87 (m, 3H), 2.78-2.73 (m, 1H), 1.88-1.84 (m, 1H), 1.76-1.72 (m, 2H), 0.97 (d, *J* = 2.5 Hz, 3H), 0.96 (d, *J* = 3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 134.1, 126.5, 124.6, 118.7, 57.4, 51.1, 49.5, 41.3, 27.1, 26.2, 23.6; $[\alpha]_D^{30}$ = +11.5 (*c* = 0.038 in isopropanol); TOF–MS (ESI+); m/z calcd. for $C_{13}H_{18}N_2S$ (M+1) 235.12, Found 235.0; Anal. Calcd. For $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95, S, 13.68. Found: C, 66.58; H, 7.69; N, 11.87, S, 13.61; HPLC (CHIRALPAK OD, *i*-PrOH/ Hexane = 10/90, Flow rate 0.8 mL/ min, λ = 254 nm): t (major) = 18.02 min, t (minor) = 13.46 min, er = 65:35.

Synthesis of 5 and 6: Compound 5 and 6 were synthesised from compound **4** according to the procedure described in reference no. 10.

Characterization of **5**; IR (cm^{-1}): 3450, 2555, 1751.2, 1631.1, 1594.0, 1436.5, 1187.6, 880.3, 867.2, 845.8, 774.1; ^1H NMR (200 MHz, D_2O): δ 7.62 (d, *J* = 8.0, 1H), 7.62-7.48 (m, 3H), 7.28

(d, *J* = 5.0, 1H), 6.7 (d, *J* = 5.0, 1H), 5.61 (s, 1H), 4.4-4.0 (m, 2H), 3.76 (s, 3 H), 3.65-3.79 (m, 2 H), 3.18 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$); δ 136.4, 132.6, 130.3, 130.2, 128.9, 126.2, 124.7, 122.5, 115.1, 58.1, 49.2, 47.6, 26.3.

Optical rotation of compound **6**: $[\alpha]_D^{30}$ = +32.1 (*c* = 0.038 in MeOH); Reported in literature $[\alpha]_D^{20}$ = +42.0 (*c* = 1 in MeOH). [9c]

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Supporting Information Available: ^{1}H and ^{13}C spectra, and HPLC chromatograms for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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