

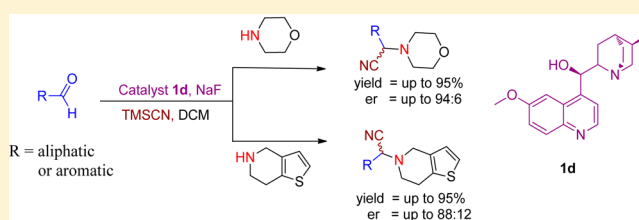
Modified Asymmetric Strecker Reaction of Aldehyde with Secondary Amine: A Protocol for the Synthesis of *S*-Clopidogrel (An Antiplatelet Agent)

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S Supporting Information

ABSTRACT: A first approach for catalytic asymmetric Strecker reaction of aldehydes with a 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 -Aminonitriles¹ are useful intermediates for the synthesis of pharmaceutically important chiral amino acids² 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} organocatalysts,⁴ and metal complexes.⁵ However, 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 has not been reported, though a few reports are available in the literature⁶ for its racemic version. Harwood et al. have reported diastereoselective 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 the cyanide source, which gave the product with a diastereomeric ratio (up to 15.4:1) that was most likely substrate driven. Herein, we report 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–e** 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 the 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 CH₂Cl₂ as solvent at –20 °C for 16 h, the product formed was in trace quantities (Table 1, entry 1). On the addition of sodium fluoride (10 mol %) to the above reaction, there was sizable improvement in the product yield (89%) and enantioselectivity (er, 73:27) (entry 2) under the same reaction condition. The

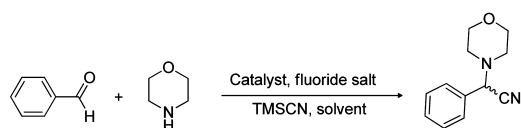
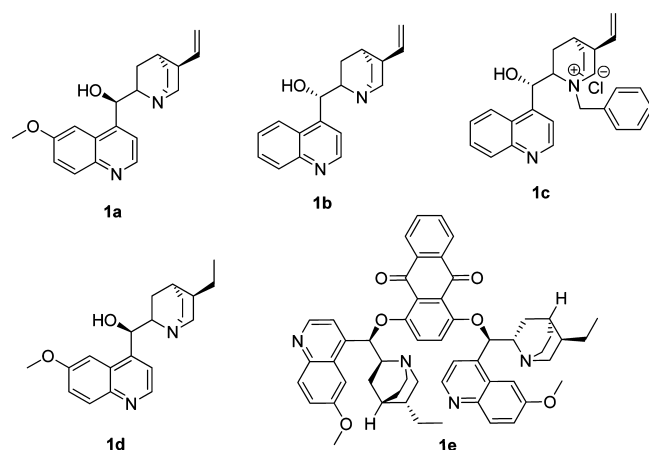
consideration of NaF as an additive was based on the strong affinity of fluoride ion toward the silicon, which was envisaged to facilitate the polarization of the Si–CN bond of TMSCN. In fact, when the above model reaction was conducted in the absence of quinine, but in the presence of NaF the product (racemic) formed in good yield (entry 3). Next, we screened other related alkaloids **1b–e** for their catalytic ability toward the above model Strecker reaction keeping other reaction parameters constant (entries 4–7). Among these alkaloids, **1d** was found to be a 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 CH₂Cl₂ at –20 °C 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 °C) gave the product in lower yield but with no improvement in the enantioselectivity (entry 9). Hence, –20 °C was taken as preferred temperature to see the effect of solvent on this reaction (entries 10–12); however, none of these (toluene, THF and CH₃CN) could match the performance of CH₂Cl₂ (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, NH₄F, and (*t*-Bu)₄NF was evaluated under the above optimized condition (entries 13–16) where NaF was found to be most effective.

The scope of the present Strecker protocol was extended to various substituted benzaldehydes, naphthaldehyde, cyclo-

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Table 1. Screening of the Catalysts for the Catalytic Modified Asymmetric Strecker Reaction^a with Secondary Amine

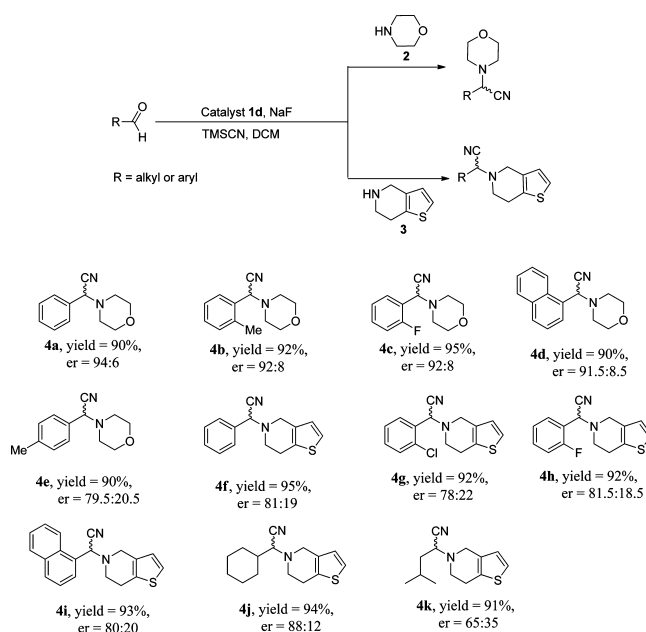


entry	catalyst	solvent	fluoride salt	yield (%) ^b	er ^c
1	1a	dichloromethane		trace	ND
2	1a	dichloromethane	NaF	89	73:27
3	-	dichloromethane	NaF	82	
4	1b	dichloromethane	NaF	82	66:34
5	1c	dichloromethane	NaF	85	70:30
6	1d	dichloromethane	NaF	90	82:18
7	1e	dichloromethane	NaF	80	54:46
8	1d^d	dichloromethane	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 ₄ F	85	75:25
16	1d	dichloromethane	TBAF	92	88:12

^aReagents and conditions: benzaldehyde (0.032 g, 0.3 mmol), morpholine (0.028 g, 0.32 mmol), catalyst (30 mol %), NaF (10 mol %), and dichloromethane (0.8 mL) were taken, and TMSCN (1.2 equiv) was added over 3 h at -20°C (total reaction time 16 h).
^bIsolated yield. ^cDetermined by HPLC analysis on chiral OD column.
^dSolid NaF and TMSCN were simultaneously added slowly over 3 h.
^eReaction was carried out at -40°C .

hexylcarboxaldehyde 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-chlorobenzaldehyde with secondary amine **3** was of particular interest as its product gave antiplatelet agent (*S*)-clopidogrel⁹ (er 78:22) in two steps¹⁰ (Scheme 2) against the 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 catalyzed by several organocatalysts like *L*-proline, *L*-Boc-phenylalanine, (*S*)-man-

Scheme 1. Scope of the Catalytic Modified Asymmetric Strecker Reaction with Secondary Amine



delic acid, *L*-diethyl tartarate, (*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).

In order to demonstrate the suggested influence of fluoride on TMSCN ¹H, ¹³C, and ²⁹Si NMR spectra of TMSCN in the presence of NaF were recorded in CDCl₃ (Figure 1). All three methyl groups of TMSCN (spectrum a) that appeared as a singlet at 0.23 ppm in ¹H NMR were downfield shifted by 40.5 Hz on the addition of NaF (0.31 ppm, spectrum b). This phenomenon was also seen in ¹³C NMR where the 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 ²⁹Si NMR, where a clear downfield shifting of Si signal of TMSCN from -11.10 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 ²⁹Si signal of (CH₃)₃SiF would have appeared at 30 ppm.¹¹ Consequently, it can be suggested that NaF is merely assisting in polarizing the Si-CN bond in order to facilitate the transfer of CN to the substrate iminium ion.

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 a 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 CH₂Cl₂ (0.8 mL) was cooled to -20°C to which TMSCN (0.36 mmol) and 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

Scheme 2. Synthetic Utility of the Product: Synthesis of (S)-Clopidogrel

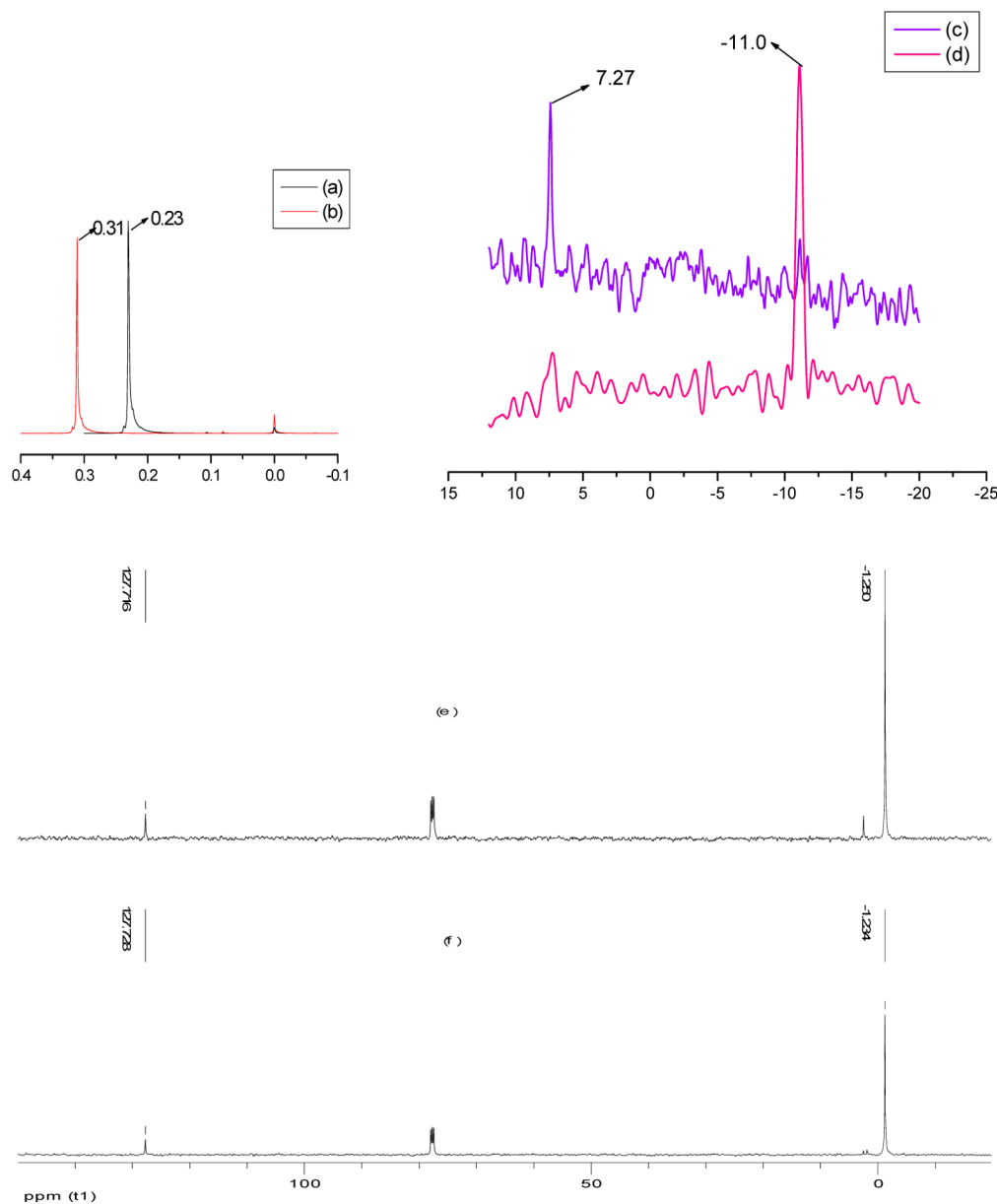
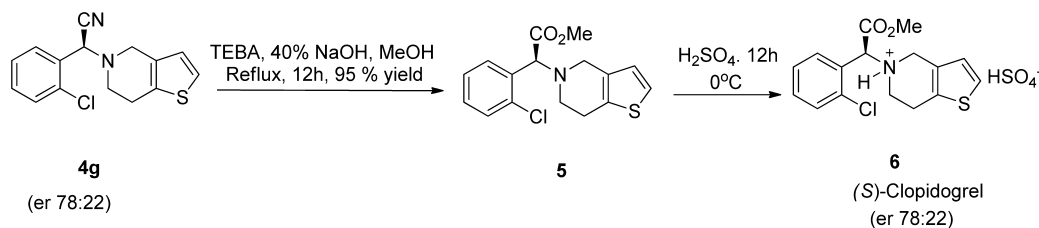


Figure 1. NMR comparison (a) ^1H NMR of TMSCN; (b) TMSCN + NaF; (c) ^{29}Si NMR of TMSCN + NaF; (d) ^{29}Si NMR of TMSCN; (e) ^{13}C NMR of TMSCN; (f) ^{13}C NMR of TMSCN + NaF.

filtered by passing through a pad of Celite and washed with water (3×15 mL) followed by brine, and the organic layer was separated and dried with anhydrous Na_2SO_4 . The solution was filtered and 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-phenylacetonitrile (4a): 55 mg, 90% yield, white solid (amorphous); mp $70\text{--}72^\circ\text{C}$; ^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; $[\alpha]_{\text{D}}^{30} = -28.2$ ($c = 0.035$ in 2-propanol); TOF-MS (ESI+) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$ ($M + 1$) 203.11, found 203.12; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 254$ nm) t_{R} (major) = 9.94 min, t_{R} (minor) = 10.79 min, er = 94:6. 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;

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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{13}H_{16}N_2O$ ($M + 1$) 217.13, found 217.11; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.6 mL/min, $\lambda = 254$ nm) t_R (major) = 19.78 min, t_R (minor) = 22.58 min, er = 92:8. 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.

2-(2-Fluorophenyl)-2-morpholinoacetonitrile (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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{12}H_{13}FN_2O$ ($M + 1$) 221.10, found 221.11; HPLC (CHIRALPAK AD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 247$ nm) t_R (major) = 17.88 min, t_R (minor) = 19.20 min, er = 92:8. 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;

2-Morpholino-(2-naphthalen-1-yl)acetonitrile (4d): 68 mg, 90% yield, white solid (amorphous); mp 128–130 °C; 1H 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{16}H_{16}N_2O$ 252.13, found 252.11; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 247$ nm) t_R (major) = 9.99 min, t_R (minor) = 8.96 min, er = 91.5:8.5. 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;

2-Morpholino-2-(p-tolyl)acetonitrile (4e): 58 mg, 90% yield, white solid (amorphous); mp 91–93 °C; 1H 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{13}H_{16}N_2O$ ($M + 1$) 217.13, found 217.12; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 254$ nm) t_R (major) = 7.73 min, t_R (minor) = 7.23 min, er = 79.5:20.5. 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;

2-(6,7-Dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-phenylacetonitrile (4f): 72 mg, 95% yield, white solid (amorphous); mp 84–86 °C; 1H 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, $J = 14.0$ Hz, 1H), 3.66 (d, $J = 14.0$ Hz, 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{15}H_{14}N_2S$ 254.09, found 254.10; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 247$ nm) t_R (major) = 16.88 min, t_R (minor) = 12.06 min, er = 81:19. 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;

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 °C; 1H 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, $J = 15.5$ Hz, 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 2-propanol); 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, $\lambda = 247$ nm) t_R (major) = 8.36 min, t_R (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 °C; 1H 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{15}H_{13}FN_2S$ ($M + 1$) 289.05, found 289.00; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 247$ nm): t_R (major) = 12.56 min, t_R (minor) = 11.65 min, er = 81.5:18.5. 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;

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 °C; 1H 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{19}H_{16}N_2S$ ($M + 1$) 305.11, found 305.10; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.6 mL/min, $\lambda = 274$ nm) t_R (major) = 8.50 min, t_R (minor) = 7.85 min, er = 80:20. 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;

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 °C; 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, $J = 15.0$ Hz, 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, $J = 15.0$ Hz, 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{15}H_{20}N_2S$ ($M + 1$) 261.14, found 261.10; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 254$ nm): t_R (major) = 9.80 min, t_R (minor) = 8.88 min, er = 88:12. 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;

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, $J = 7.5$ Hz, 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 2-propanol); TOF-MS (ESI+) m/z calcd for $C_{13}H_{18}N_2S$ ($M + 1$) 235.12, found 235.0; HPLC (CHIRALPAK OD, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 254$ nm): t_R (major) = 18.02 min, t_R (minor) = 13.46 min, er = 65:35. 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;

Synthesis of 5 and 6. Compound 5 and 6 were synthesized from compound 4 according to the procedure described in ref 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, $J = 8.0$ Hz, 1H), 7.62–7.48 (m, 3H), 7.28 (d, $J = 5.0$ Hz, 1H), 6.7 (d, $J = 5.0$ Hz, 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) [lit.^{9c} $[\alpha]_D^{20} = +42.0$ ($c = 1$ in MeOH)].

■ ASSOCIATED CONTENT

■ Supporting Information

¹H proton coupled and proton decoupled ¹³C and DEPT 135 NMR 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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Notes

The authors declare no competing financial interest.

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