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Cinchona-based primary amine-catalyzed enantioselective aza-Michael reactions of pyrroles with α,β-unsaturated aldehydes

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ABSTRACT

The cinchona-based primary amine-catalyzed enantioselective aza-Michael reaction of α,β-unsaturated aldehydes with 4,5-dihalo-1*H*-pyrrole-2-carbonitriles as the *N*-centered heteroaromatic nucleophile, followed by chemoselective reduction provided the corresponding chiral aza-Michael products in good yields and with excellent enantioselectivities (90–97% ee).

1. Introduction

Pyrrole is one of the most ubiquitous heterocycles found in natural products[1] and pharmaceuticals[2] that exhibit various appealing biological properties. Due to the prevalence of pyrroles, the synthesis of enantioenriched *C*-alkylated pyrroles via organocatalytic routes has been a subject of active research.[3] Recently, we reported on the organocatalytic asymmetric aza-Michael reaction[4] of pyrroles as an *N*-centered heteroaromatic nucleophile[5] with TBDPS-protected (*E*)-4-hydroxybut-2-enal using chiral diarylprolinol trimethylsilyl ether[6] as the secondary amine catalyst[7] and benzoic acid as the acid additive (Fig. 1),[5c] and its application as the key step in the enantioselective formal synthesis of bromopyrrole alkaloid natural products. Due to the importance of enantiopure *N*-alkylated pyrroles as pharmacophores in biologically active natural products,[1] we sought to further develop the aza-Michael reaction of pyrroles with an expanded scope of α,β-unsaturated aldehydes in the presence of various chiral primary amine catalysts[8–10] to show the applicability of these organocatalysts in this synthetic route. Although chiral primary amine-catalyzed asymmetric aza-Michael reactions of α,β-unsaturated ketones with *N*-centered heteroaromatic nucleophiles have been reported,[5b,11] to the best of our knowledge the corresponding use of α,β-unsaturated aldehydes as substrates has not been reported. For the successful progress of this organocatalytic reaction, the pK_a of the pyrrole NH should be sufficiently low to be deprotonated by a base to generate the resulting nucleophilic pyrrole anion.[5] Herein we report a cinchona-based primary amine-catalyzed enantioselective aza-Michael reaction of various α,β-unsaturated aldehydes with 4,5-dihalo-1*H*-pyrrole-2-carbonitriles, followed by a chemoselective reduction that affords the corresponding chiral aza-Michael products with excellent enantioselectivities (Fig. 1).

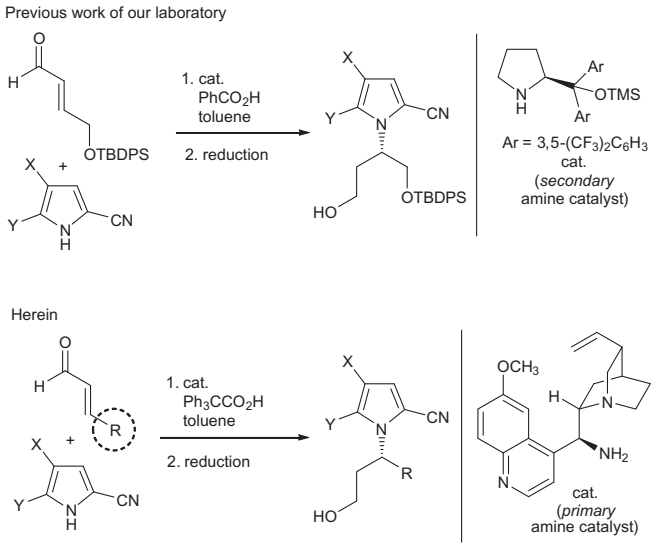

Figure 1. Organocatalytic asymmetric aza-Michael reactions of pyrroles with α,β-unsaturated aldehydes.

2. Results and discussion

In order to explore the feasibility of chiral primary amine-catalyzed enantioselective aza-Michael reactions of α,β-unsaturated aldehydes with pyrroles, we investigated the aza-Michael reaction

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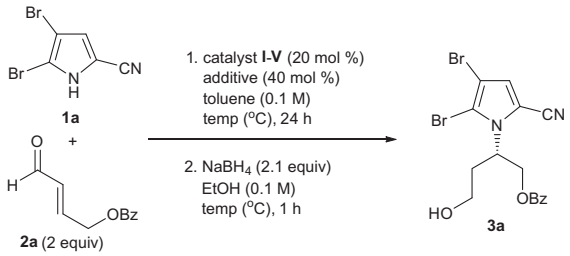
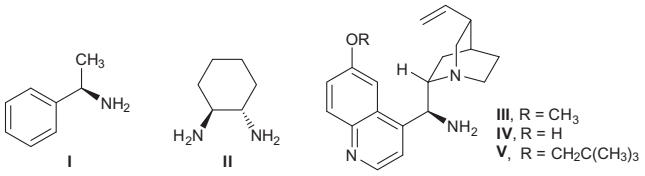
Table 1
Optimization of chiral primary amine-catalyzed enantioselective aza-Michael reactions of 4,5-dibromo-1*H*-pyrrole-2-carbonitrile **1a** with (*E*)-4-oxobut-2-enyl benzoate **2a**[a]





Entry	Cat.	Additive	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	**I**	$PhCO_2H$	0	56	0
2	**II**	$PhCO_2H$	0	56	0
3	**III**	$PhCO_2H$	0	59	62
4	**IV**	$PhCO_2H$	0	54	56
5	**V**	$PhCO_2H$	0	56	54
6	**III**	$PhCO_2H$	−20	50	88
7	**III**	$PhCO_2H$	−30	21	93
8	**III**	CH_3CO_2H	−20	23	85
9	**III**	4-NO_2–$C_6H_4CO_2H$	−20	41	90
10	**III**	Ph_3CCO_2H	−20	62	90
11[d]	**III**	Ph_3CCO_2H	−30	56	90

[a] Procedure: **2a** (0.4 mmol) was added to a mixture of **1a** (0.2 mmol), catalyst (0.04 mmol), and additive (0.08 mmol) in toluene (2 mL) in one portion. The reaction mixture was stirred at 0, −20, or −30 °C for 24 or 48 h, at which point the aldehyde was directly reduced to an alcohol with $NaBH_4$ (0.42 mmol) in EtOH (2 mL).
[b] Isolated yield for two steps.
[c] Determined by HPLC analysis (Chiralpak AD-H).
[d] For 48 h.

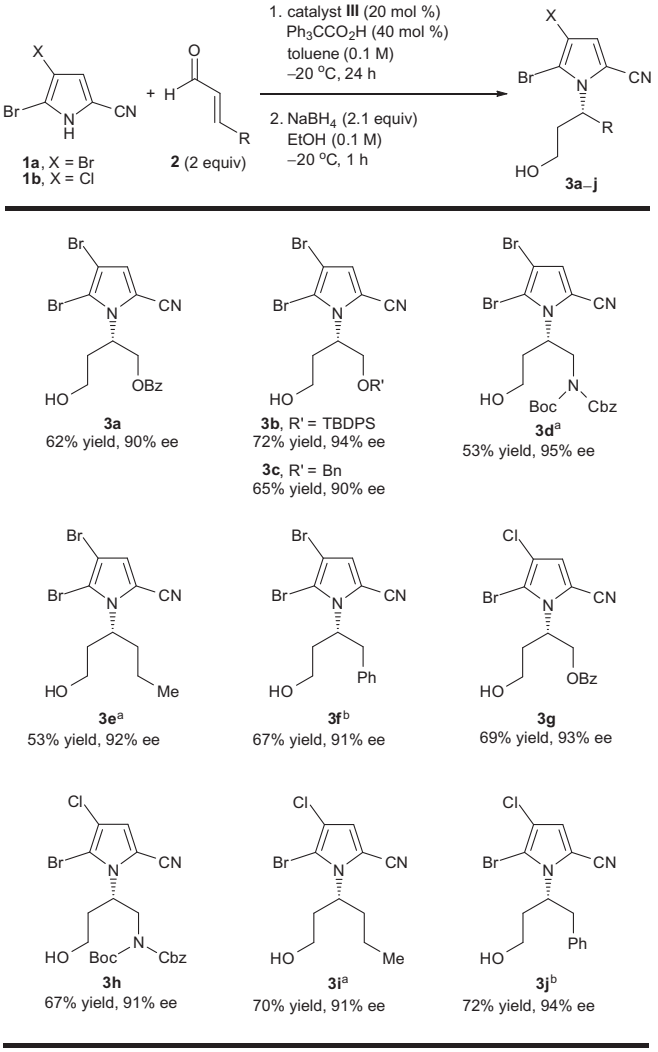


Figure 2. Organocatalytic enantioselective aza-Michael reactions of 5-bromo-4-halo-1*H*-pyrrole-2-carbonitriles **1a**,**b** with various α,β-unsaturated aldehydes **2**. The cited yields are of isolated products obtained over two steps. The ee values were determined by chiral HPLC analysis (Chiralcel OD-H, Chiralcel OJ-H, or Chiralpak AD-H). [a]3 equiv of **2** were used at −30 °C. [b]3 equiv of **2** were used.

of 4,5-dibromo-1*H*-pyrrole-2-carbonitrile **1a** with (*E*)-4-oxobut-2-enyl benzoate **2a** using $PhCO_2H$ (40 mol %) as the acid additive in toluene at 0 °C, in the presence of catalysts **I**–**V** (Table 1). The product was isolated as alcohol **3a** following $NaBH_4$ reduction of the aza-Michael aldehyde product. Among the organocatalysts assayed (Table 1, entries 1–5), catalyst **III** proved to be the best and afforded the desired aza-Michael product **3a** in 59% yield with 62% ee. Lowering the reaction temperature with **III** to −20 °C provided **3a** in 50% yield with 88% ee (Table 1, entry 6). Lowering the temperature further to −30 °C gave **3a** with an increased ee of 93%, but with a considerably decreased yield of 21% (Table 1, entry 7). Finally, among the additives tested, Ph_3CCO_2H was seen to be ideal for the reaction, and **3a** was obtained in 62% yield with 90% ee (Table 1, entries 8–10).[12] However, in case of the reaction at −30 °C for 48 h under otherwise identical conditions, **3a** was obtained in a decreased yield of 56%, while sustaining the ee at 90% (Table 1, entry 11).

Subsequently, the scope of α,β-unsaturated aldehydes **2** amenable to the organocatalytic enantioselective aza-Michael reaction with 5-bromo-4-halo-1*H*-pyrrole-2-carbonitriles **1a**,**b** was explored under the optimized conditions (Fig. 2). The reaction of **1a** with an assortment of α,β-unsaturated aldehydes bearing variously protected hydroxyalkyl, doubly *N*-protected aminoalkyl, aliphatic, and aromatic-substituted alkyl substituents afforded the desired aza-Michael products **3a**–**f** in good yields and with excellent enantioselectivities. The dibromopyrrole moiety incorporated in **3a**–**f** was found to be in an important class of marine natural products that show various interesting biological properties.[13] Similarly, **1b** underwent the aza-Michael reaction with various α,β-unsaturated aldehydes bearing Bz-protected hydroxyalkyl, doubly *N*-protected aminoalkyl, aliphatic, and aromatic-substituted alkyl substituents to provide the desired products **3g**–**j** in good yields and excellent enantioselectivities.

Further exploration of the organocatalytic enantioselective aza-Michael reactions with 4-bromo-5-iodo-1*H*-pyrrole-2-carbonitrile **1c** was then carried out by varying the α,β-unsaturated aldehydes **2** (Fig. 3). Following our reaction conditions for the chemoselective reductions of the aza-Michael aldehyde products generated from 4-halo-5-iodo-1*H*-pyrrole-2-carbonitriles,[5c] the $NaBH_4$ reduction of the products generated from **1c** led to the reduction of the iodo group, as well as the aldehyde, to afford alcohols **3k**–**m**. Conversely, the reduction of the same aza-Michael aldehyde products using $BH_3{\cdot}SMe_2$ in THF provided the alcohol products **3n**–**p** without any reduction of the iodo group. In all cases, the corresponding aza-Michael products **3k**–**p** were obtained in good yields and with excellent enantioselectivities. In addition, the halo groups on the pyrrole moiety in **3a**–**p** can be used in carbon—carbon bond

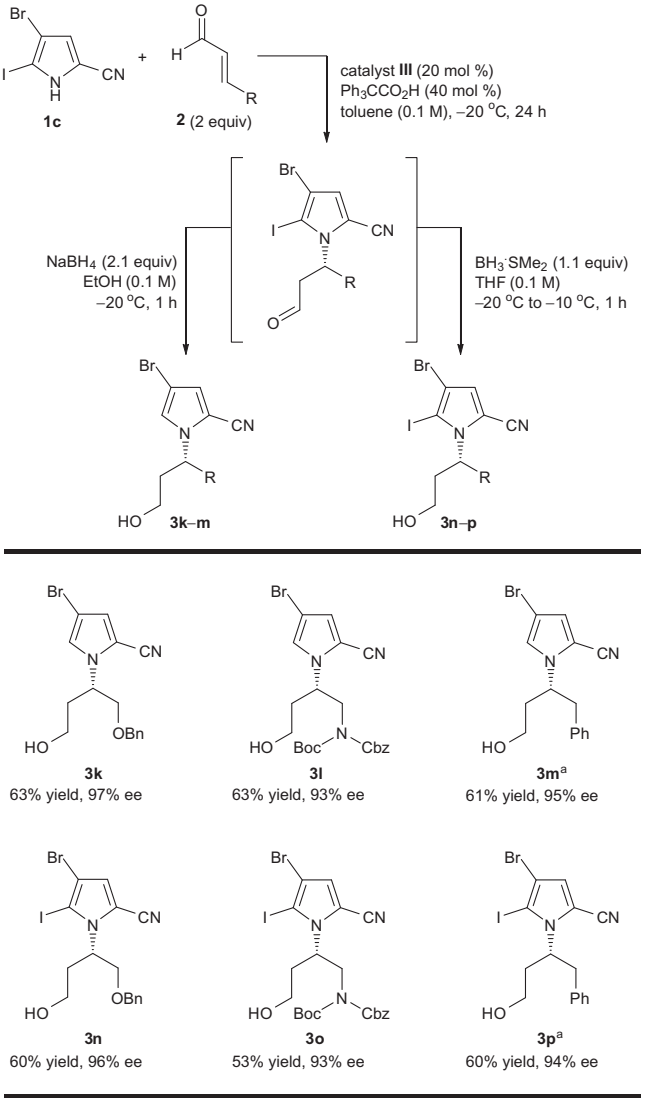


Figure 3. Organocatalytic enantioselective aza-Michael reactions followed by chemoselective reductions of 4-bromo-5-iodo-1*H*-pyrrole-2-carbonitrile **1c** with various α,β-unsaturated aldehydes **2**. The cited yields are of isolated products obtained over two steps. The ee values were determined by chiral HPLC analysis (Chiralcel OD-H, Chiralcel OJ-H, or Chiralpak AD-H). [a]3 equiv of **2** were used.

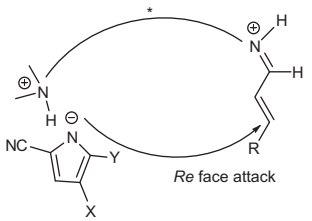


Figure 4. Proposed transition state of the aza-Michael reaction.

forming reactions to synthesize a variety of potentially biologically active pyrrole-based compounds.[14] Some of the aza-Michael products consist of two conformers, according to analysis of ^{1}H and ^{13}C NMR spectra, which may be explained by the hindered internal rotation due to the steric interactions among the pyrrole substituents.[15]

The absolute stereochemical assignment of all aza-Michael products was based on the absolute stereochemistry of **3a**, which was determined to be (*S*)-configured by comparing the specific rotation of **3a** with that reported in the literature.[5c] From this obtained absolute stereochemistry, the proposed transition state of the aza-Michael reaction is briefly outlined as shown in Figure 4. The aza-Michael addition of the anionic pyrrole nucleophile from the *Re* face of the iminium intermediate,[16] generated from the reaction of the amino group of the cinchona-based primary amine catalyst **III** with the α,β-unsaturated aldehyde in the presence of Ph_3CCO_2H, provided the desired product.

3. Conclusion

In conclusion, the cinchona-based primary amine-catalyzed enantioselective aza-Michael reaction of α,β-unsaturated aldehydes with 4,5-dihalo-1*H*-pyrrole-2-carbonitriles using Ph_3CCO_2H as the acid additive, followed by chemoselective reduction provided the corresponding chiral aza-Michael products in good yields and with excellent enantioselectivities (90–97% ee). This is the only example of the use of α,β-unsaturated aldehydes as substrates in chiral primary amine-catalyzed asymmetric aza-Michael reactions with *N*-centered heteroaromatic nucleophiles. This synthetic strategy provides an efficient route for generating various enantioenriched *N*-alkylated pyrroles as core structures of biologically active natural products and pharmaceutical agents. Further studies will focus on the application of these species to the synthesis of biologically potent compounds.

4. Experimental

4.1. General

The NMR spectroscopic data were recorded with a Bruker 400 MHz spectrometer using tetramethylsilane as the internal reference. Mass spectra data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. Enantiomeric excess values were determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H, OJ-H, or Chiralpak AD-H).

4.2. Materials

Pyrroles **1**[13b,c,17] and α,β-unsaturated aldehydes **2**[18] were prepared according to reported procedures.

4.3. General procedure for the organocatalytic enantioselective aza-Michael reactions

To a mixture of pyrrole **1** (0.2 mmol), catalyst **III** (0.04 mmol), and Ph_3CCO_2H (0.08 mmol) in toluene (2 mL) was added α,β-unsaturated aldehyde **2** (0.4 mmol) in one portion. The reaction mixture was allowed to stir at −20 °C for 24 h, at which point the aldehyde was directly reduced with either $NaBH_4$ (0.42 mmol) in EtOH (2 mL) or $BH_3{\cdot}SMe_2$ (0.22 mmol) in THF (2 mL) to the alcohol. After 1 h, the reaction was quenched by saturated aqueous $NaHCO_3$. The mixture was poured into ethyl acetate, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The organic layer was filtered off and evaporated. The crude residue was purified by silica gel column chromatography.

4.3.1. (*S*)-2-(2,3-Dibromo-5-cyano-1*H*-pyrrol-1-yl)-4-hydroxybutyl benzoate 3a

Colorless oil (55 mg, 62%); $[\alpha]_D^{22}$ = +6.9 (*c* 1, CH_3OH) 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.2 Hz, 2H), 7.59–7.54 (m, 1H),

7.44–7.41 (m, 2H), 6.99 (s, 1H), 5.32–5.22 (m, 1H), 4.82–4.67 (m, 2H), 3.82–3.79 (m, 1H), 3.54–3.47 (m, 1H), 2.58–2.46 (m, 1H), 2.35–2.23 (m, 1H), 1.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 133.3, 129.6, 128.9, 128.4, 124.3, 113.7, 112.7, 102.7, 99.5, 65.2, 58.0, 57.3, 32.7; FTIR (neat) 3557, 2945, 2218, 1716, 1412, 1326, 1312, 1263, 1120, 705 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{14}Br_2N_2O_3$ 439.9371, found 439.9373; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 0.9 mL/min, λ = 254 nm) 23.7 min (minor isomer), 26.0 min (major isomer).

4.3.2. (*S*)-4,5-Dibromo-1-[1-(*tert*-butyldiphenylsilyloxy)-4-hydroxybutan-2-yl]-1*H*-pyrrole-2-carbonitrile 3b

White solid (83 mg, 72%); mp 99–101 °C; $[\alpha]_D^{24}$ = +20.4 (*c* 1, CH_3OH) 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.52–7.35 (m, 8H), 6.92 (s, 1H), 5.07–4.96 (m, 1H), 4.11 (t, *J* = 10.0 Hz, 1H), 3.92–3.88 (m, 1H), 3.70–3.63 (m, 1H), 3.47–3.38 (m, 1H), 2.34–2.27 (m, 1H), 2.08–2.02 (m, 1H), 1.38 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.6, 132.3, 129.9, 129.8, 127.7, 123.8, 114.2, 112.8, 102.4, 99.0, 65.0, 60.3, 58.3, 32.3, 26.4, 18.9; FTIR (neat) 3368, 2928, 2858, 2223, 1416, 1310, 1112, 699 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}Br_2N_2O_2Si$ 574.0287, found 574.0286; HPLC (Chiralpak AD-H, Hexane/IPA = 95:5, 1.0 mL/min, λ = 254 nm) 8.8 min (minor isomer), 9.9 min (major isomer).

4.3.3. (*S*)-1-[1-(Benzyloxy)-4-hydroxybutan-2-yl]-4,5-dibromo-1*H*-pyrrole-2-carbonitrile 3c

Colorless oil (56 mg, 65%); $[\alpha]_D^{24}$ = +3.2 (*c* 1, $CHCl_3$) 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 3H), 7.21–7.19 (m, 2H), 6.91 (s, 1H), 5.08–4.99 (m, 1H), 4.57–4.44 (m, 2H), 4.00–3.96 (m, 1H), 3.80–3.76 (m, 1H), 3.73–3.68 (m, 1H), 3.46–3.41 (m, 1H), 2.39–2.30 (m, 1H), 2.17–2.09 (m, 1H), 1.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 128.3, 127.7, 127.4, 123.8, 113.6, 112.8, 102.4, 99.1, 72.9, 70.6, 58.2, 58.2, 33.0; FTIR (neat) 3436, 2925, 2869, 2219, 1413, 1312, 1093, 738 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{16}Br_2N_2O_2$ 425.9579, found 425.9580; HPLC (Chiralpak AD-H, Hexane/IPA = 95:5, 0.9 mL/min, λ = 254 nm) 33.4 min (major isomer), 36.6 min (minor isomer).

4.3.4. (*S*)-1-[1-[(Benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino]-4-hydroxybutan-2-yl]-4,5-dibromo-1*H*-pyrrole-2-carbonitrile 3d

Mixture of two conformers (major/minor = 83:17), colorless oil (61 mg, 53%); $[\alpha]_D^{25}$ = +61.2 (*c* 1, $CHCl_3$) 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5H), 6.78 and 6.69 (major: s, minor: s, 1H), 5.24–4.93 (m, 3H), 4.50 and 4.46 (minor: dd, *J* = 14.8, 9.6 Hz, major: dd, *J* = 14.8, 10.4 Hz, 1H), 3.93 and 3.90 (minor: dd, *J* = 14.4, 3.6 Hz, major: dd, *J* = 14.8, 3.2 Hz, 1H), 3.74–3.67 (m, 1H), 3.50–3.39 (m, 1H), 2.46–2.31 (m, 1H), 2.25–2.16 (m, 1H), 1.64 and 1.59 (minor: t, *J* = 5.2 Hz, major: t, *J* = 5.2 Hz, 1H), 1.41 and 1.39 (minor: s, major: s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 153.2, 151.3, 134.8, 128.7, 128.5, 128.4, 123.6, 113.2, 112.9, 103.6, 98.9, 83.8, 68.8, 58.3, 57.7, 49.1, 33.9, 27.7, minor conformer: δ 153.2, 151.4, 135.0, 128.6, 128.4, 128.4, 120.8, 111.4, 108.8, 108.5, 101.7, 84.0, 68.8, 59.2, 58.6, 48.1, 33.3, 27.7; FTIR (neat) 3510, 2978, 2930, 2221, 1736, 1694, 1339, 1308, 1217, 1142, 1107, 751 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{22}H_{25}Br_2N_3O_5$ 569.0161, found 569.0164; HPLC (Chiralcel OJ-H, Hexane/IPA = 90:10, 0.95 mL/min, λ = 254 nm) 14.5 min (minor isomer), 19.1 min (major isomer).

4.3.5. (*R*)-4,5-Dibromo-1-(1-hydroxyhexan-3-yl)-1*H*-pyrrole-2-carbonitrile 3e

Mixture of two conformers (major/minor = 81:19), colorless oil (37 mg, 53%); $[\alpha]_D^{25}$ = −12.2 (*c* 1, $CHCl_3$) 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 and 6.82 (major: s, minor: s, 1H), 4.81–4.75 (m, 1H), 3.66–3.61 (m, 1H), 3.39–3.33 (m, 1H), 2.45–2.32 (m, 1H), 2.22–2.07 (m, 2H), 1.85–1.76 (m, 1H), 1.64 (s, 1H), 1.31–1.18 (m, 1H), 1.16–1.03 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 123.9, 113.1, 112.9, 102.2, 98.8, 58.6, 58.5, 36.9, 36.6, 19.3, 13.5; FTIR (neat) 3431, 2959, 2931, 2873, 2219, 1411, 1379, 1309, 1047, 804 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{11}H_{14}Br_2N_2O$ 347.9473, found 347.9472; HPLC (Chiralcel OD-H, Hexane/IPA = 95:5, 0.8 mL/min, λ = 220 nm) 14.7 min (minor isomer), 18.4 min (major isomer).

4.3.6. (*R*)-4,5-Dibromo-1-(4-hydroxy-1-phenylbutan-2-yl)-1*H*-pyrrole-2-carbonitrile 3f

Mixture of two conformers (major/minor = 80:20), colorless oil (53 mg, 67%); $[\alpha]_D^{25}$ = +58.0 (*c* 1, $CHCl_3$) 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.09–7.05 (m, 2H), 6.93 and 6.60 (major: s, minor: s, 1H), 5.06–4.93 (m, 1H), 3.70–3.67 (m, 1H), 3.51–3.32 (m, 2H), 3.21–3.13 (m, 1H), 2.66–2.60 and 2.54–2.46 (minor: m, major: m, 1H), 2.24–2.16 (m, 1H), 1.44 and 1.36 (minor: s, major: s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 136.1, 128.7, 128.5, 127.0, 123.9, 113.3, 113.2, 102.1, 98.7, 60.1, 58.4, 40.8, 36.2, minor conformer: δ 136.1, 128.6, 128.6, 127.0, 120.4, 111.6, 108.7, 107.0, 101.7, 61.6, 58.5, 39.5, 35.1; FTIR (neat) 3442, 2927, 2219, 1411, 1311, 1045, 751, 699 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{14}Br_2N_2O$ 395.9473, found 395.9473; HPLC (Chiralpak AD-H, Hexane/IPA = 95:5, 0.8 mL/min, λ = 254 nm) 24.6 min (minor isomer), 27.3 min (major isomer).

4.3.7. (*S*)-2-(2-Bromo-3-chloro-5-cyano-1*H*-pyrrol-1-yl)-4-hydroxybutyl benzoate 3g

Colorless oil (55 mg, 69%); $[\alpha]_D^{22}$ = −2.8 (*c* 1, $CHCl_3$) 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 2H), 7.59–7.54 (m, 1H), 7.44–7.41 (m, 2H), 6.92 (s, 1H), 5.29–5.19 (m, 1H), 4.84–4.66 (m, 2H), 3.82–3.79 (m, 1H), 3.53–3.48 (m, 1H), 2.58–2.47 (m, 1H), 2.34–2.24 (m, 1H), 1.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 133.3, 129.5, 128.9, 128.4, 121.6, 113.9, 112.8, 111.2, 101.7, 65.1, 58.0, 56.9, 32.6; FTIR (neat) 3502, 2925, 2219, 1719, 1315, 1266, 1109, 708 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{14}BrClN_2O_3$ 395.9876, found 395.9872; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 0.9 mL/min, λ = 254 nm) 21.9 min (minor isomer), 23.3 min (major isomer).

4.3.8. (*S*)-1-[1-[(Benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino]-4-hydroxybutan-2-yl]-5-bromo-4-chloro-1*H*-pyrrole-2-carbonitrile 3h

Mixture of two conformers (major/minor = 82:18), colorless oil (71 mg, 67%); $[\alpha]_D^{22}$ = +70.8 (*c* 1, $CHCl_3$) 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5H), 6.73 and 6.63 (major: s, minor: s, 1H), 5.24–4.91 (m, 3H), 4.50 and 4.46 (minor: dd, *J* = 14.8, 9.6 Hz, major: dd, *J* = 14.8, 10.4 Hz, 1H), 3.93 and 3.90 (minor: dd, *J* = 14.4, 3.6 Hz, major: dd, *J* = 14.8, 3.2 Hz, 1H), 3.74–3.68 (m, 1H), 3.49–3.39 (m, 1H), 2.47–2.31 (m, 1H), 2.25–2.16 (m, 1H), 1.65 and 1.59 (minor: t, *J* = 5.2 Hz, major: t, *J* = 5.2 Hz, 1H), 1.41 and 1.39 (minor: s, major: s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 153.2, 151.3, 134.8, 128.7, 128.5, 128.4, 121.0, 113.4, 113.0, 110.7, 102.7, 83.8, 68.8, 58.2, 57.3, 49.0, 33.8, 27.7, minor conformer: δ 153.2, 151.4, 134.9, 128.6, 128.4, 128.4, 118.0, 115.7, 111.5, 107.7, 106.1, 84.0, 68.8, 59.2, 58.6, 48.1, 33.3, 27.7; FTIR (neat) 3512, 2977, 2930, 2220, 1736, 1694, 1339, 1314, 1143, 1107, 752 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{22}H_{25}BrClN_3O_5$ 525.0666, found 525.0667; HPLC (Chiralcel OJ-H, Hexane/IPA = 90:10, 0.95 mL/min, λ = 254 nm) 16.3 min (minor isomer), 22.3 min (major isomer).

4.3.9. (*R*)-5-Bromo-4-chloro-1-(1-hydroxyhexan-3-yl)-1*H*-pyrrole-2-carbonitrile 3i

Mixture of two conformers (major/minor = 81:19), colorless oil (43 mg, 70%); $[\alpha]_D^{20}$ = −13.2 (*c* 1, $CHCl_3$) 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 and 6.76 (major: s, minor: s, 1H), 4.78–4.73 (m, 1H), 3.68–3.63 (m, 1H), 3.41–3.33 (m, 1H), 2.52–2.33 (m, 1H), 2.24–2.07

(m, 2H), 1.85–1.77 (m, 1H), 1.43 (s, 1H), 1.33–1.21 (m, 1H), 1.16–1.03 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 121.2, 113.2, 113.0, 110.6, 101.2, 58.5, 58.1, 36.9, 36.5, 19.3, 13.5; FTIR (neat) 3429, 2959, 2930, 2218, 1416, 1386, 1316, 1047, 802 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{11}H_{14}BrClN_2O$ 303.9978, found 303.9981; HPLC (Chiralcel OD-H, Hexane/IPA = 95:5, 0.9 mL/min, λ = 254 nm) 12.5 min (minor isomer), 15.9 min (major isomer).

4.3.10. (*R*)-5-Bromo-4-chloro-1-(4-hydroxy-1-phenylbutan-2-yl)-1*H*-pyrrole-2-carbonitrile 3j

Mixture of two conformers (major/minor = 80:20), colorless oil (51 mg, 72%); $[\alpha]_D^{20}$ = +67.0 (c 1, $CHCl_3$) 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.09–7.05 (m, 2H), 6.86 and 6.54 (major: s, minor: s, 1H), 5.03–4.94 (m, 1H), 3.71–3.67 (m, 1H), 3.51–3.32 (m, 2H), 3.22–3.17 (m, 1H), 2.66–2.57 and 2.55–2.46 (minor: m, major: m, 1H), 2.26–2.17 (m, 1H), 1.43 and 1.34 (minor: s, major: s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 136.1, 128.7, 128.5, 127.0, 121.2, 113.3, 113.1, 110.9, 101.2, 59.6, 58.4, 40.7, 36.2, minor conformer: δ 136.1, 128.6, 128.6, 127.0, 117.7, 115.7, 111.8, 107.7, 104.6, 61.5, 58.6, 39.5, 35.1; FTIR (neat) 3436, 2926, 2217, 1416, 1387, 1317, 1046, 753, 699 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{14}BrClN_2O$ 351.9978, found 351.9982; HPLC (Chiralpak AD-H, Hexane/IPA = 95:5, 0.9 mL/min, λ = 254 nm) 19.7 min (minor isomer), 21.6 min (major isomer).

4.3.11. (*S*)-1-[1-(Benzyloxy)-4-hydroxybutan-2-yl]-4-bromo-1*H*-pyrrole-2-carbonitrile 3k

Colorless oil (44 mg, 63%); $[\alpha]_D^{22}$ = −28.1 (c 1, $CHCl_3$) 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 3H), 7.25–7.22 (m, 2H), 6.99 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 1.6 Hz, 1H), 4.68–4.62 (m, 1H), 4.56–4.45 (m, 2H), 3.75–3.69 (m, 2H), 3.68–3.62 (m, 1H), 3.47–3.41 (m, 1H), 2.17–2.02 (m, 2H), 1.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.4, 127.8, 127.6, 124.9, 120.9, 112.5, 104.6, 96.3, 73.2, 71.5, 58.2, 56.6, 34.3; FTIR (neat) 3439, 2926, 2867, 2219, 1453, 1316, 1094, 1078, 1047, 737, 697 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{17}BrN_2O_2$ 348.0473, found 348.0475; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 1.0 mL/min, λ = 254 nm) 11.0 min (minor isomer), 12.9 min (major isomer).

4.3.12. (*S*)-1-[1-[(Benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino]-4-hydroxybutan-2-yl]-4-bromo-1*H*-pyrrole-2-carbonitrile 3l

Colorless oil (62 mg, 63%); $[\alpha]_D^{22}$ = +44.7 (c 1, $CHCl_3$) 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 6.81 (d, J = 1.6 Hz, 1H), 6.66 (d, J = 1.6 Hz, 1H), 5.21–5.10 (m, 2H), 4.80–4.72 (m, 1H), 4.19 (dd, J = 14.4, 9.6 Hz, 1H), 3.90 (dd, J = 14.4, 4.0 Hz, 1H), 3.68–3.63 (m, 1H), 3.47–3.41 (m, 1H), 2.11–1.98 (m, 2H), 1.58 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 151.4, 134.9, 128.5, 128.4, 128.4, 124.6, 121.1, 112.1, 105.1, 96.6, 83.9, 68.9, 58.2, 56.5, 49.9, 34.9, 27.7; FTIR (neat) 3541, 2926, 2224, 1740, 1726, 1332, 1116, 757 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{22}H_{26}BrN_3O_5$ 491.1056, found 491.1057; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 1.0 mL/min, λ = 254 nm) 13.2 min (minor isomer), 17.8 min (major isomer).

4.3.13. (*R*)-4-Bromo-1-(4-hydroxy-1-phenylbutan-2-yl)-1*H*-pyrrole-2-carbonitrile 3m

Colorless oil (39 mg, 61%); $[\alpha]_D^{22}$ = +74.3 (c 1, $CHCl_3$) 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.19 (m, 3H), 7.02–6.99 (m, 2H), 6.79 (d, J = 1.6 Hz, 1H), 6.66 (d, J = 1.6 Hz, 1H), 4.68–4.61 (m, 1H), 3.67–3.62 (m, 1H), 3.43–3.36 (m, 1H), 3.15–3.04 (m, 2H), 2.21–2.04 (m, 2H), 1.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 128.7, 128.6, 127.0, 123.9, 120.9, 112.4, 104.3, 96.2, 59.0, 58.3, 42.4, 37.1; FTIR (neat) 3437, 2924, 2218, 1455, 1380, 1315, 1044, 752, 699 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{15}BrN_2O$ 318.0368, found 318.0370; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 1.0 mL/min, λ = 254 nm) 8.9 min (minor isomer), 11.3 min (major isomer).

4.3.14. (*S*)-1-[1-(Benzyloxy)-4-hydroxybutan-2-yl]-4-bromo-5-iodo-1*H*-pyrrole-2-carbonitrile 3n

Colorless oil (57 mg, 60%); $[\alpha]_D^{20}$ = −4.4 (c 1, $CHCl_3$) 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 3H), 7.22–7.20 (m, 2H), 6.98 (s, 1H), 5.02–4.92 (m, 1H), 4.57–4.44 (m, 2H), 3.98 (dd, J = 9.6, 9.2 Hz, 1H), 3.79 (dd, J = 10.4, 5.2 Hz, 1H), 3.70–3.68 (m, 1H), 3.44–3.39 (m, 1H), 2.39–2.33 (m, 1H), 2.18–2.10 (m, 1H), 1.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 128.3, 127.7, 127.4, 124.4, 112.7, 106.4, 104.5, 88.7, 73.0, 70.9, 61.4, 58.2, 33.3; FTIR (neat) 3430, 2924, 2868, 2217, 1395, 1373, 1321, 1305, 1093, 1049, 735 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{16}BrN_2O_2I$ 473.9440, found 473.9438; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 1.0 mL/min, λ = 254 nm) 17.4 min (major isomer), 22.2 min (minor isomer).

4.3.15. (*S*)-1-[1-[(Benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino]-4-hydroxybutan-2-yl]-4-bromo-5-iodo-1*H*-pyrrole-2-carbonitrile 3o

Mixture of two conformers (major/minor = 93:7), colorless oil (66 mg, 53%); $[\alpha]_D^{20}$ = +53.2 (c 1, $CHCl_3$) 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5H), 6.86 and 6.72 (major: s, minor: s, 1H), 5.23–4.92 (m, 3H), 4.54 and 4.50 (minor: dd, J = 14.8, 9.6 Hz, major: dd, J = 14.8, 10.4 Hz, 1H), 3.94 and 3.89 (minor: dd, J = 14.8, 3.6 Hz, major: dd, J = 14.8, 2.8 Hz, 1H), 3.73–3.66 (m, 1H), 3.48–3.37 (m, 1H), 2.56–2.48 and 2.39–2.31 (minor: m, major: m, 1H), 2.30–2.16 (m, 1H), 1.68 and 1.63 (minor: t, J = 5.2 Hz, major: t, J = 5.2 Hz, 1H), 1.41 and 1.38 (minor: s, major: s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 153.2, 151.2, 134.8, 128.9, 128.5, 128.4, 124.2, 112.8, 106.2, 105.6, 88.2, 83.7, 68.8, 61.0, 58.2, 49.2, 34.2, 27.7, minor conformer: δ 153.2, 151.5, 134.9, 128.6, 128.4, 128.4, 120.7, 111.9, 111.3, 109.4, 88.2, 84.0, 68.8, 59.6, 58.6, 48.3, 33.8, 27.7; FTIR (neat) 3509, 2962, 2928, 2219, 1736, 1693, 1369, 1339, 1298, 1217, 1139, 1106, 751 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{22}H_{25}BrN_3O_5I$ 617.0022, found 617.0021; HPLC (Chiralcel OD-H, Hexane/IPA = 90:10, 1.0 mL/min, λ = 254 nm) 18.1 min (minor isomer), 26.3 min (major isomer).

4.3.16. (*R*)-4-Bromo-1-(4-hydroxy-1-phenylbutan-2-yl)-5-iodo-1*H*-pyrrole-2-carbonitrile 3p

Mixture of two conformers (major/minor = 90:10), light yellow oil (53 mg, 60%); $[\alpha]_D^{22}$ = +45.1 (c 1, $CHCl_3$) 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.09–7.04 (m, 2H), 7.00 and 6.63 (major: s, minor: s, 1H), 5.06–4.98 and 4.95–4.87 (minor: m, major: m, 1H), 3.69–3.56 (m, 1H), 3.43–3.32 (m, 2H), 3.20–3.12 (m, 1H), 2.80–2.71 and 2.57–2.48 (minor: m, major: m, 1H), 2.23–2.15 (m, 1H), 1.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major conformer: δ 136.1, 128.9, 128.5, 127.0, 124.4, 113.1, 106.0, 104.2, 88.5, 63.2, 58.3, 41.0, 36.3, minor conformer: δ 136.2, 128.6, 128.6, 127.0, 120.5, 112.0, 111.5, 109.4, 88.5, 61.8, 58.6, 39.6, 35.2; FTIR (neat) 3437, 2927, 2216, 1393, 1371, 1303, 1044, 751, 699 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{14}BrN_2OI$ 443.9334, found 443.9336; HPLC (Chiralpak AD-H, Hexane/IPA = 90:10, 1.0 mL/min, λ = 254 nm) 12.8 min (major isomer), 15.5 min (minor isomer).

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