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Asymmetric Synthesis of Chiral Pyrrolizine-Based Triheterocycles by Organocatalytic Cascade Aza-Michael–Aldol Reactions

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Keywords: Organocatalysis / Asymmetric catalysis / Domino reactions / Heterocycles / Polycycles

New, chiral pyrrolizine-based triheterocycles were obtained by the organocatalytic asymmetric cascade aza-Michael–aldol reaction of α-branched α,β-unsaturated aldehydes with 2-(trifluoroacetyl)pyrroles. High enantioselectivities (90–95 % *ee*) and excellent diastereoselectivities (*dr* up to >20:1) were achieved by employing this synthetic strategy. The highly functionalized, trifluoromethyl-substituted cascade products have three consecutive stereogenic centers that include two chiral quaternary centers. The chemoselective stepwise Suzuki cross-coupling reaction of the cascade products with two different arylboronic acids provided chiral pyrrolizine-based triheterocycles that contain two distinct aryl substituents in good yields.

Introduction

Methods for the construction of polyheterocyclic skeletons have been the focus of intensive research efforts because of the structural features and interesting biological activities of these molecules.[1] In particular, the development of efficient routes for the asymmetric synthesis of stereogenic complex compounds, which include chiral polyheterocycles, from simple precursors in a single step has become a challenging topic in modern organic chemistry.[2] In this regard, we recently reported the organocatalytic asymmetric cascade aza-Michael–aldol reactions of α,β-unsaturated carbonyl compounds with pyrroles as the *N*-centered heteroaromatic nucleophiles to provide a variety of chiral pyrrolizines (see Figure 1).[3] Because of the importance of pyrrolizines to the development of antitumor,[4] antileukemic,[5] and anti-inflammatory agents,[6] we plan to synthesize unprecedented pyrrolizine-based polyheterocycles as potential scaffolds for pharmaceutical preparations. Herein, we report the organocatalytic asymmetric cascade aza-Michael–aldol reaction[7,8] of the α-branched α,β-unsaturated aldehydes such as cyclopent-1-enecarbaldehyde and 4,5-dihydrofuran-2-carbaldehyde with 2-(trifluoroacetyl)pyrroles as the *N*-centered heteroaromatic nucleophiles (see Figure 1). Our synthetic strategy provides unique and highly functionalized chiral pyrrolizine-based triheterocycles with three consecutive stereogenic centers that include two chiral quaternary centers.

The incorporation of a trifluoromethyl group into a molecule is known to improve the biological and pharmacolog-

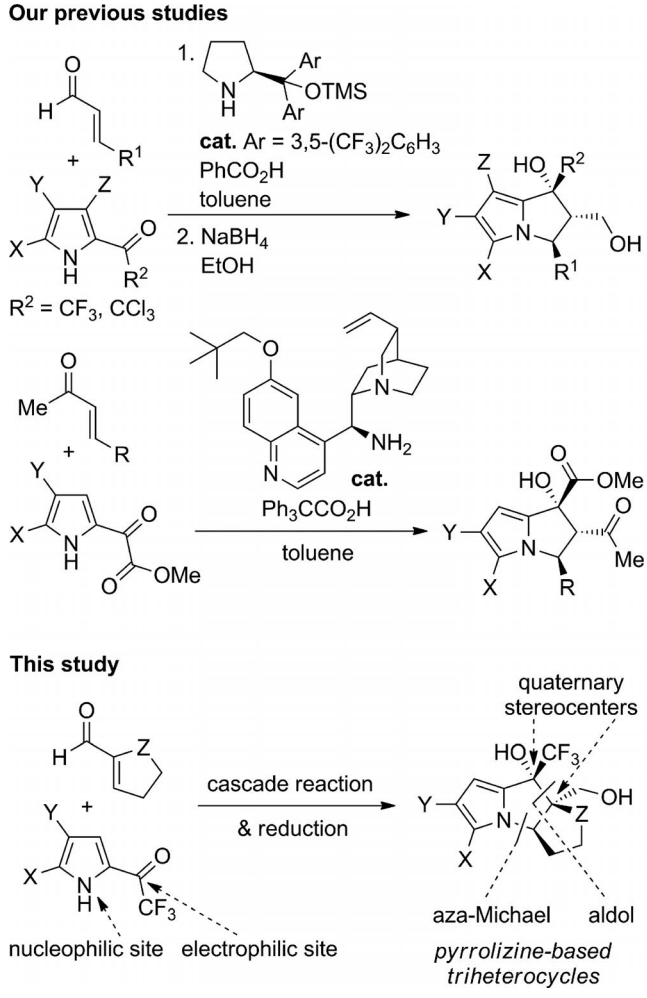

Figure 1. Organocatalytic asymmetric cascade aza-Michael–aldol reactions of pyrroles with enals and enones.

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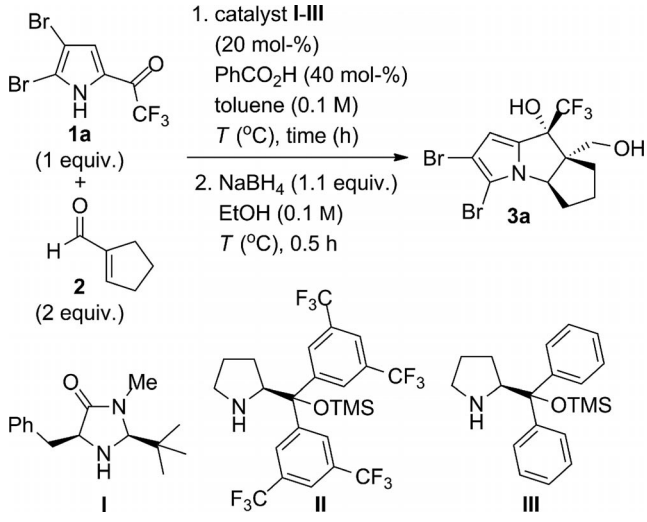
ical properties of bioactive compounds.[9] For the success of this cascade reaction, the pK_a value of the NH of the pyrrole should be sufficiently low for deprotonation by a base to generate the requisite anionic pyrrole nucleophile,[3,10] which will undergo the initial aza-Michael reaction[11] with the α-branched α,β-unsaturated aldehyde. In addition, the carbonyl group of the trifluoroacetyl moiety of the pyrrole should serve as the electrophile for the subsequent aldol reaction. Concomitantly, the chemoselective stepwise Suzuki cross-coupling reactions of the cascade products with two different arylboronic acids provide the chiral pyrrolizine-based triheterocycles that contain two distinct aryl substituents.

Results and Discussion

To explore the feasibility of the organocatalytic asymmetric cascade reaction of α-branched α,β-unsaturated aldehydes with 2-(trifluoroacetyl)pyrroles, the cascade reaction of 1-(4,5-dibromo-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethanone (**1a**) with cyclopent-1-enecarbaldehyde (**2**) with $PhCO_2H$ (40 mol-%) as the acid additive in toluene at 0 °C were performed in the presence of chiral organocatalysts **I** and **II** (TMS = trimethylsilyl), respectively (see Table 1, Entries 1 and 2). Although catalyst **I** gave no corresponding product, catalyst **II** provided the desired cascade product **3a** as a single diastereomer in 57% yield and with 33%*ee*. All of the products from these cascade reactions were obtained after the in situ reduction of the cascade aldehyde product with $NaBH_4$ in EtOH to give the alcohol. Upon lowering the reaction temperature to –40 °C, cascade product **3a** showed a considerable increase of the *ee* value to 95%, but the yield decreased to 26% (see Table 1, Entries 3 and 4). Varying the reaction time revealed that 96 h was ideal for these cascade reactions, and **3a** was obtained in 50% yield with 94%*ee* (see Table 1, Entries 5 and 6). Finally, when the loading of **2** was increased to 3 equiv. under otherwise identical conditions, the highly functionalized chiral pyrrolizine-based triheterocycle **3a** was obtained as a single diastereomer in 74% yield and with 93%*ee* (see Table 1, Entry 7).[12] When catalyst **II** was replaced by **III**, cascade product **3a** was obtained with an *ee* value of 94%, but the yield decreased to 38% (see Table 1, Entries 6 vs. 8).

Subsequently, a range of 2-(trifluoroacetyl)pyrroles **1** were explored as the nucleophiles in the enantio- and diastereoselective organocatalytic cascade aza-Michael–aldol reaction with cyclopent-1-enecarbaldehyde (**2**) under the optimized conditions. A series of 2-(trifluoroacetyl)pyrroles that contain various substituents such as a 4,5-dihalo or a 4-nitro group were examined (see Scheme 1). In all cases, the chiral pyrrolizine-based triheterocycles **3a**–**3i** were obtained in good yields and with excellent enantioselectivities. In addition, with regard to the diastereoselectivity of the reaction to give chiral cascade products **3a**–**3i**, all products with the exception of **3i**, which was produced with a *dr* of 17.5:1, were obtained as single diastereomers. The halo groups on the pyrrole moiety of cascade products **3a**–**3h** can be employed in carbon–carbon coupling reactions to provide a wide variety of chiral pyrrolizine-based triheterocycles.[13] In particular, the dibromopyrrole moiety of **3a** is found in an important class of natural products that exhibit a variety of appealing biological activities.[14]

Table 1. Optimization of organocatalytic asymmetric cascade aza-Michael–aldol reaction of 1-(4,5-dibromo-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethanone (**1a**) with cyclopent-1-enecarbaldehyde (**2**).[a]

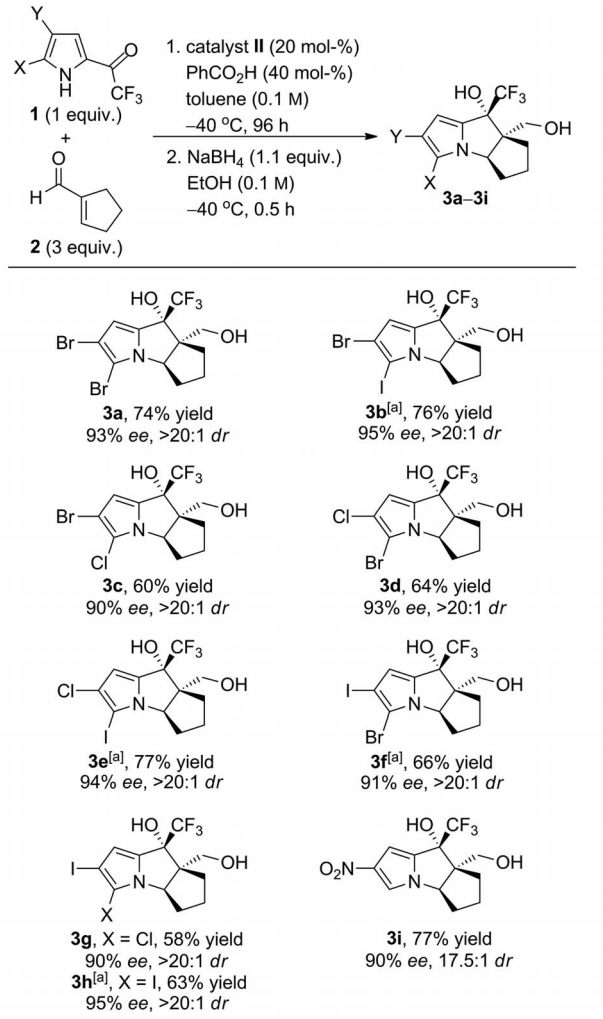


Entry	Catalyst	*T* [°C]	Time [h]	% Yield[b]	% *ee*[c]	*dr*[d]
1	**I**	0	48	n.r.[e]	–	–
2	**II**	0	48	57	33	>20:1
3	**II**	–20	48	43	80	>20:1
4	**II**	–40	48	26	95	>20:1
5	**II**	–40	72	38	95	>20:1
6	**II**	–40	96	50	94	>20:1
7[f]	**II**	–40	96	74	93	>20:1
8	**III**	–40	96	38	94	>20:1

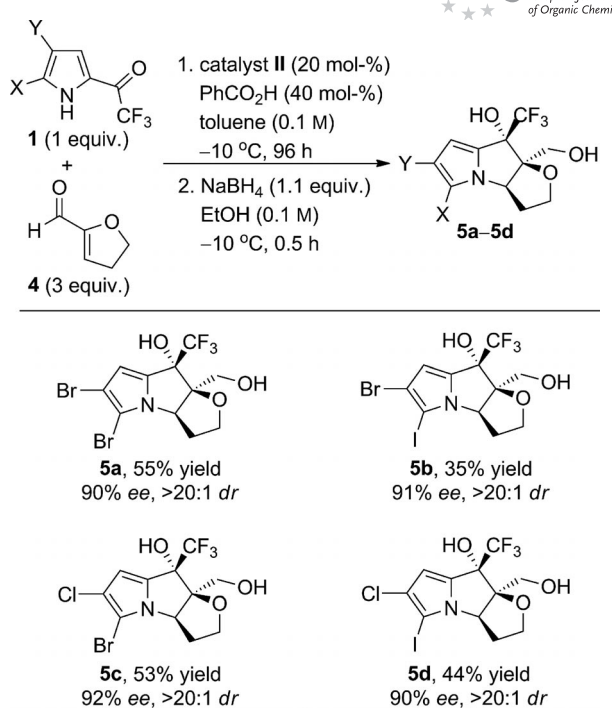
[a] Reagents and conditions: **2** (0.4 mmol) was added to a mixture of **1a** (0.2 mmol), catalyst (0.04 mmol), and $PhCO_2H$ (0.08 mmol) in toluene (2 mL) in one portion. The reaction mixture was stirred at 0, –20, or –40 °C for 48, 72, or 96 h, at which point the aldehyde was directly reduced to an alcohol with $NaBH_4$ (0.22 mmol) in EtOH (2 mL). [b] Isolated yield for two steps. [c] Determined by chiral HPLC analysis (Chiralpak AD-H). [d] Diastereomeric ratio (*dr*) determined by ^{1}H NMR spectroscopy. [e] n.r.: no reaction. [f] 3 equiv. of **2** was used.

To expand the scope of the α-branched α,β-unsaturated aldehydes employed in the organocatalytic asymmetric cascade reactions, the reactions between 4,5-dihydrofuran-2-carbaldehyde (**4**) and a series of 1-(4,5-dihalo-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethanones **1** were performed at –10 °C under otherwise identical conditions (see Scheme 2). In all cases, the desired cascade products **5a**–**5d** were obtained as single diastereomers and with excellent enantioselectivities, but the yields were somewhat lower in comparison to those obtained from the reaction with **2**. This decrease of reactivity is a result of the electronic effects of the oxygen atom on the 4,5-dihydrofuranyl ring of **4**.

In an effort to expand the molecular diversity of the chiral pyrrolizine-based triheterocycles, chemoselective stepwise Suzuki cross-coupling reactions of the cascade prod-

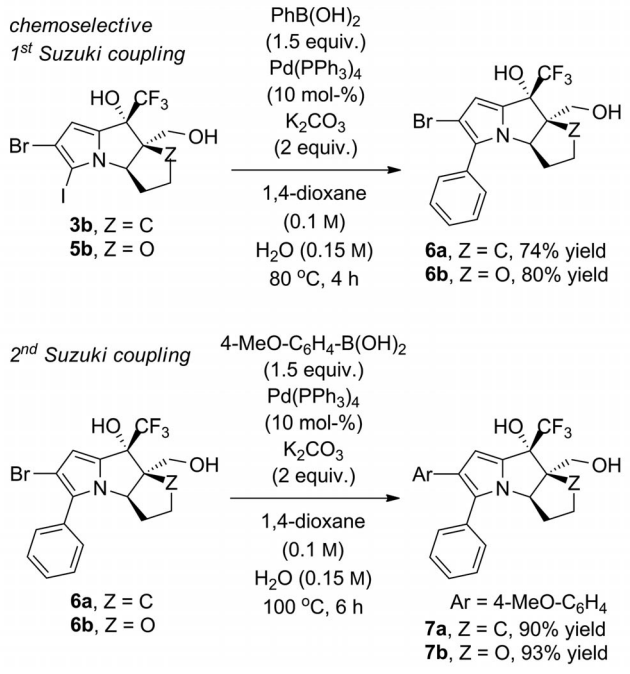


Scheme 1. Organocatalytic asymmetric cascade aza-Michael–aldol reaction of cyclopent-1-enecarbaldehyde (**2**) with various 2-(trifluoroacetyl)pyrroles **1** (see Exp. Section for detailed procedure). Reported yields are of isolated products obtained over two steps. Enantiomeric excess values were determined by chiral HPLC analysis (Chiralpak AD-H). Diastereomeric ratios were determined by ^{1}H NMR spectroscopy. [a] Reaction at –30 °C.



Scheme 2. Organocatalytic asymmetric cascade aza-Michael–aldol reaction of 4,5-dihydrofuran-2-carbaldehyde (**4**) with various 2-(trifluoroacetyl)pyrroles **1** (see Exp. Section for detailed procedures). Reported yields are of isolated products obtained over two steps. Enantiomeric excess values were determined by chiral HPLC analysis (Chiralcel OD-H, Chiralcel OJ-H, or Chiralpak AD-H). Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

ucts were carried out with two different arylboronic acids (see Scheme 3). On the basis of our previous reaction conditions for chemoselective Suzuki cross-coupling reactions of dihalopyrrolizines,[13a] the chemoselective Suzuki cross-coupling reactions of **3b** and **5b** with phenylboronic acid (1.5 equiv.) were performed in the presence of $Pd(PPh_3)_4$ (10 mol-%) and K_2CO_3 (2 equiv.) in a solution of 1,4-dioxane/H_2O at 80 °C for 4 h. These reactions afforded the 6-bromo-5-phenyl-substituted pyrrolizine-based triheterocycles **6a** and **6b**, respectively, as the desired coupling products in good yields without the 5-iodo-6-phenyl-substituted pyrrolizine-based triheterocycle byproducts. Next, the sequential second Suzuki cross-coupling reactions of **6a** and **6b** were carried out under otherwise identical conditions with 4-methoxyphenylboronic acid at 100 °C for 6 h to obtain the desired unsymmetrical 5,6-diaryl-substituted chiral pyrrolizine-based triheterocycles **7a** and **7b**, respectively, in good yields.



Scheme 3. Synthesis of chiral pyrrolizine-based triheterocycles that contain two different aryl substituents through the chemoselective stepwise Suzuki cross-coupling reactions of **3b** and **5b**.

The absolute stereochemical assignments of all the cascade products were made on the basis of the single-crystal X-ray diffraction analysis of pyrrolizine-based triheterocycle **3b** (see Figure 2).[15] From the absolute stereochemistry of the cascade products, the proposed catalytic cycle, which includes the course of the asymmetric induction of the cascade reaction, is described in Scheme 4. The aza-Michael reaction of the iminium intermediate,[16] which is generated from the chiral diarylprolinol trimethylsilyl ether catalyst[17] and the α-branched α,β-unsaturated aldehyde in the presence of $PhCO_2H$, with the anionic pyrrole nucleophile affords the aza-Michael intermediate. The subsequent intramolecular aldol reaction of the aza-Michael intermediate followed by hydrolysis provides the desired cascade product.

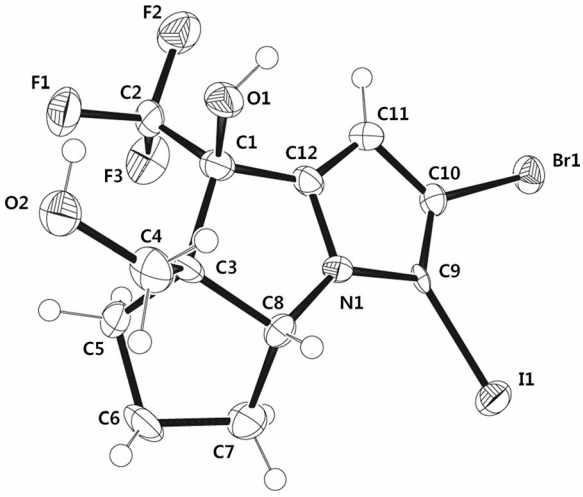
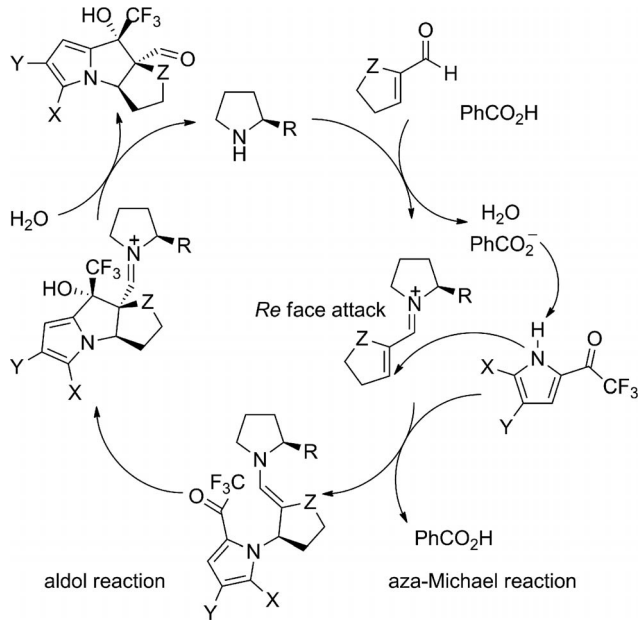


Figure 2. The molecular structure of **3b** as determined by single-crystal X-ray diffraction analysis.



Scheme 4. Proposed catalytic cycle of the organocatalytic asymmetric cascade aza-Michael–aldol reaction.

Conclusions

Unique and chiral pyrrolizine-based triheterocycles were obtained by the enantio- and diastereoselective cascade aza-Michael–aldol reactions of the α-branched α,β-unsaturated aldehydes such as cyclopent-1-enecarbaldehyde and 4,5-dihydrofuran-2-carbaldehyde with 2-(trifluoroacetyl)pyrroles using chiral diarylprolinol trimethylsilyl ether **II** as the organocatalyst and benzoic acid as the acid additive. High enantioselectivities (90–95% *ee*) and excellent diastereoselectivities (*dr* up to >20:1) were achieved by employing this synthetic strategy. The highly functionalized and trifluoromethyl-substituted cascade products have three consecutive stereogenic centers that include two chiral quaternary centers. In addition, the chemoselective stepwise Suzuki cross-coupling reactions of the cascade products with two different arylboronic acids afforded chiral pyrrolizine-based triheterocycles that contain two distinct aryl substituents in good yields. This strategy provides an efficient route for the stereoselective synthesis of a variety of chiral pyrrolizine-based triheterocycles, which are potential scaffolds for pharmaceutical agents. The application of these triheterocycles to the syntheses of biologically potent compounds will be a topic of further studies.

Experimental Section

General Methods: The NMR spectroscopic data were recorded with a Bruker 400 MHz spectrometer using tetramethylsilane as the internal reference. Mass spectroscopic data were obtained from the Korea Basic Science Institute (Daegu) with 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, Chiralcel OJ-H, or Chiralpak AD-H). Pyrroles **1**,[13c,18] cyclopent-1-enecarbaldehyde (**2**),[19] and 4,5-dihydrofuran-2-carbaldehyde (**4**)[20] were prepared according to reported procedures.

General Procedure for the Organocatalytic Asymmetric Cascade Aza-Michael–Aldol Reactions of α-Branched α,β-Unsaturated Aldehydes with 2-(Trifluoroacetyl)pyrroles: α-Branched α,β-unsaturated aldehyde **2** (0.6 mmol) was added in one portion to a mixture of **1** (0.2 mmol), catalyst **II** (0.04 mmol), and $PhCO_2H$ (0.08 mmol) in toluene (2 mL). The reaction mixture was stirred at –30 or –40 °C for 96 h. Then, the aldehyde was directly reduced to the alcohol by the addition of $NaBH_4$ (0.22 mmol) in EtOH (2 mL). The reaction mixture was stirred for 0.5 h and then it was warmed to room temp. and quenched by the addition of saturated $NaHCO_3$. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and then dried with $MgSO_4$. Filtration of the organic layer followed by evaporation of the solvents gave the crude residue, which was purified by silica gel column chromatography to provide the desired cascade product **3**. This general procedure was applied to α-branched α,β-unsaturated aldehyde **4** at –10 °C under otherwise identical conditions to provide the desired cascade product **5**.

(3a*R*,8*R*,8a*S*)-5,6-Dibromo-8a-(hydroxymethyl)-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3a): White solid (62 mg, 74%); m.p. 77–79 °C. $[\alpha]_D^{19}$ = –51.0 (*c* = 1, CH_3OH);

93%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (s, 1 H), 4.86 (dd, J = 6.8, 3.6 Hz, 1 H), 4.05 (dd, J = 12.0, 3.6 Hz, 1 H), 3.60 (dd, J = 12.0, 8.8 Hz, 1 H), 3.53 (s, 1 H), 2.93 (dd, J = 8.8, 4.4 Hz, 1 H), 2.30–2.21 (m, 1 H), 2.20–2.11 (m, 1 H), 2.09–2.01 (m, 1 H), 1.81–1.74 (m, 2 H), 1.62–1.54 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.8, 124.5 (q, $^1J_{C,F}$ = 282.0 Hz), 105.4, 101.6, 98.9, 80.5 (q, $^2J_{C,F}$ = 30.0 Hz), 65.9, 65.4, 64.5, 31.2, 30.3 (q, $^3J_{C,F}$ = 3.0 Hz), 25.3 ppm. FTIR (neat): $\tilde{\nu}$ = 3559, 3257, 2961, 1703, 1667, 1406, 1280, 1160, 1115, 1072, 966, 796 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NBr_2F_3$ $[M]^+$ 416.9187; found 416.9189. HPLC (Chiralpak AD-H; hexane/isopropyl alcohol (IPA), 93:7; 0.9 mL/min; λ = 220 nm): t_R = 11.0 (minor isomer) and 14.5 min (major isomer).

(3a*R*,8*R*,8a*S*)-6-Bromo-8a-(hydroxymethyl)-5-iodo-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3b): White solid (71 mg, 76%); m.p. 143–145 °C. $[\alpha]_D^{22}$ = –52.0 (c = 1, CH_3OH); 95%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (s, 1 H), 4.79 (dd, J = 6.8, 4.0 Hz, 1 H), 4.05 (dd, J = 12.0, 4.0 Hz, 1 H), 3.62 (dd, J = 12.0, 8.8 Hz, 1 H), 3.41 (s, 1 H), 2.86 (dd, J = 8.8, 4.4 Hz, 1 H), 2.37–2.28 (m, 1 H), 2.13–2.02 (m, 2 H), 1.81–1.73 (m, 2 H), 1.63–1.57 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 124.5 (q, $^1J_{C,F}$ = 282.0 Hz), 109.1, 106.0, 80.5 (q, $^2J_{C,F}$ = 31.0 Hz), 67.9, 66.9, 65.3, 64.7, 32.1, 30.5 (q, $^3J_{C,F}$ = 3.0 Hz), 25.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3556, 3259, 2960, 1389, 1290, 1164, 1120, 1031, 958, 893, 795 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NBrF_3I$ $[M]^+$ 464.9048; found 464.9051. HPLC (Chiralpak AD-H; hexane/IPA, 90:10; 0.9 mL/min; λ = 254 nm): t_R = 18.7 (minor isomer) and 23.2 min (major isomer).

(3a*R*,8*R*,8a*S*)-6-Bromo-5-chloro-8a-(hydroxymethyl)-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3c): White solid (45 mg, 60%); m.p. 85–87 °C. $[\alpha]_D^{22}$ = –36.9 (c = 1, CH_3OH); 90%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 1 H), 4.90 (dd, J = 6.4, 4.0 Hz, 1 H), 4.07 (dd, J = 12.4, 4.0 Hz, 1 H), 3.62 (dd, J = 12.4, 8.8 Hz, 1 H), 3.37 (s, 1 H), 2.86 (dd, J = 8.8, 4.0 Hz, 1 H), 2.27–2.12 (m, 2 H), 2.09–2.01 (m, 1 H), 1.82–1.75 (m, 2 H), 1.60–1.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7, 124.5 (q, $^1J_{C,F}$ = 282.0 Hz), 112.5, 104.6, 97.5, 80.5 (q, $^2J_{C,F}$ = 30.0 Hz), 65.5, 65.2, 64.4, 30.5, 30.3 (q, $^3J_{C,F}$ = 3.0 Hz), 25.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3233, 2971, 1701, 1667, 1414, 1289, 1165, 1119, 1085, 1012, 945, 782 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NClBrF_3$ $[M]^+$ 372.9692; found 372.9691. HPLC (Chiralpak AD-H; hexane/IPA, 93:7; 0.9 mL/min; λ = 220 nm): t_R = 10.1 (minor isomer) and 13.8 min (major isomer).

(3a*R*,8*R*,8a*S*)-5-Bromo-6-chloro-8a-(hydroxymethyl)-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3d): White solid (48 mg, 64%); m.p. 90–92 °C. $[\alpha]_D^{22}$ = –41.0 (c = 1, CH_3OH); 93%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (s, 1 H), 4.85 (dd, J = 6.8, 4.0 Hz, 1 H), 4.06 (dd, J = 12.0, 4.0 Hz, 1 H), 3.62 (dd, J = 12.0, 8.4 Hz, 1 H), 3.43 (s, 1 H), 2.86 (dd, J = 8.4, 4.0 Hz, 1 H), 2.29–2.21 (m, 1 H), 2.19–2.11 (m, 1 H), 2.09–2.02 (m, 1 H), 1.81–1.74 (m, 2 H), 1.60–1.54 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.8, 124.5 (q, $^1J_{C,F}$ = 282.0 Hz), 116.0, 103.0, 96.5, 80.8 (q, $^2J_{C,F}$ = 30.0 Hz), 65.9, 65.3, 64.6, 31.2, 30.4 (q, $^3J_{C,F}$ = 3.0 Hz), 25.3 ppm. FTIR (neat): $\tilde{\nu}$ = 3549, 3239, 2923, 1727, 1458, 1392, 1284, 1164, 1122, 1032, 974, 899, 796 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NClBrF_3$ $[M]^+$ 372.9692; found 372.9689. HPLC (Chiralpak AD-H; hexane/IPA, 93:7; 0.9 mL/min; λ = 254 nm): t_R = 14.1 (minor isomer) and 21.6 min (major isomer).

(3a*R*,8*R*,8a*S*)-6-Chloro-8a-(hydroxymethyl)-5-iodo-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3e): White solid (65 mg, 77%); m.p. 159–161 °C. $[\alpha]_D^{22}$ = –55.0 (c = 1, CH_3OH); 94%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (s, 1 H), 4.78 (dd, J = 6.8, 4.0 Hz, 1 H), 4.06 (dd, J = 12.0, 4.0 Hz, 1 H), 3.63 (dd, J = 12.0, 8.4 Hz, 1 H), 3.33 (s, 1 H), 2.80 (dd, J = 8.4, 4.0 Hz, 1 H), 2.35–2.27 (m, 1 H), 2.14–2.03 (m, 2 H), 1.81–1.73 (m, 2 H), 1.63–1.58 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 138.7, 126.5 (q, $^1J_{C,F}$ = 282.0 Hz), 123.2, 104.5, 81.4 (q, $^2J_{C,F}$ = 30.0 Hz), 69.7, 66.1, 65.1, 64.8, 33.6, 31.3 (q, $^3J_{C,F}$ = 3.0 Hz), 26.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3547, 3246, 2961, 2882, 2620, 2418, 1376, 1286, 1173, 1148, 1031, 963, 793 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NClF_3I$ $[M]^+$ 420.9553; found 420.9554. HPLC (Chiralpak AD-H; hexane/IPA, 95:5; 0.9 mL/min; λ = 220 nm): t_R = 16.7 (minor isomer) and 22.0 min (major isomer).

(3a*R*,8*R*,8a*S*)-5-Bromo-8a-(hydroxymethyl)-6-iodo-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3f): White solid (62 mg, 66%); m.p. 87–89 °C. $[\alpha]_D^{22}$ = –61.0 (c = 1, CH_3OH); 91%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 4.88 (dd, J = 6.8, 4.0 Hz, 1 H), 4.06 (dd, J = 12.4, 4.0 Hz, 1 H), 3.62 (dd, J = 12.0, 8.8 Hz, 1 H), 3.30 (s, 1 H), 2.82 (dd, J = 8.8, 4.4 Hz, 1 H), 2.29–2.22 (m, 1 H), 2.17–2.10 (m, 1 H), 2.09–2.02 (m, 1 H), 1.81–1.74 (m, 2 H), 1.62–1.58 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 124.5 (q, $^1J_{C,F}$ = 282.0 Hz), 110.1, 103.8, 80.2 (q, $^2J_{C,F}$ = 30.0 Hz), 69.3, 65.9, 65.8, 64.6, 31.2, 30.4 (q, $^3J_{C,F}$ = 3.0 Hz), 25.3 ppm. FTIR (neat): $\tilde{\nu}$ = 3436, 3120, 2977, 1430, 1391, 1278, 1162, 1109, 1060, 949, 794 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NBrF_3I$ $[M]^+$ 464.9048; found 464.9049. HPLC (Chiralpak AD-H; hexane/IPA, 95:5; 0.95 mL/min; λ = 220 nm): t_R = 18.2 (minor isomer) and 21.0 min (major isomer).

(3a*R*,8*R*,8a*S*)-5-Chloro-8a-(hydroxymethyl)-6-iodo-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3g): White solid (49 mg, 58%); m.p. 71–73 °C. $[\alpha]_D^{22}$ = –53.0 (c = 1, CH_3OH); 90%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (s, 1 H), 4.91 (dd, J = 6.8, 4.0 Hz, 1 H), 4.05 (dd, J = 12.0, 3.6 Hz, 1 H), 3.62 (s, 1 H), 3.59 (dd, J = 12.4, 8.8 Hz, 1 H), 2.98 (dd, J = 8.8, 4.0 Hz, 1 H), 2.26–2.11 (m, 2 H), 2.08–2.01 (m, 1 H), 1.81–1.74 (m, 2 H), 1.59–1.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.8, 124.5 (q, $^1J_{C,F}$ = 282.0 Hz), 116.8, 109.2, 80.2 (q, $^2J_{C,F}$ = 30.0 Hz), 65.9, 65.2, 64.5, 64.4, 30.6, 30.4 (q, $^3J_{C,F}$ = 3.0 Hz), 25.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3474, 3233, 2970, 1441, 1407, 1279, 1168, 1111, 944, 788 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NClF_3I$ $[M]^+$ 420.9553; found 420.9555. HPLC (Chiralpak AD-H; hexane/IPA, 95:5; 0.95 mL/min; λ = 254 nm): t_R = 16.2 (minor isomer) and 19.5 min (major isomer).

(3a*R*,8*R*,8a*S*)-8a-(Hydroxymethyl)-5,6-diiodo-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3h): White solid (65 mg, 63%); m.p. 159–161 °C. $[\alpha]_D^{22}$ = –62.0 (c = 1, CH_3OH); 95%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (s, 1 H), 4.79 (dd, J = 6.8, 4.0 Hz, 1 H), 4.03 (dd, J = 12.4, 4.0 Hz, 1 H), 3.68 (s, 1 H), 3.58 (dd, J = 12.0, 8.8 Hz, 1 H), 3.02 (dd, J = 8.4, 4.0 Hz, 1 H), 2.36–2.28 (m, 1 H), 2.11–2.01 (m, 2 H), 1.84–1.71 (m, 2 H), 1.62–1.56 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 140.9, 126.5 (q, $^1J_{C,F}$ = 282.0 Hz), 112.2, 80.6 (q, $^2J_{C,F}$ = 30.0 Hz), 79.0, 74.3, 69.7, 66.6, 65.0, 33.7, 31.3 (q, $^3J_{C,F}$ = 3.0 Hz), 26.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3442, 3120, 2977, 1420, 1277, 1162, 1117, 1060, 949, 795 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}O_2NF_3I_2$ $[M]^+$ 512.8910; found 512.8910. HPLC (Chiralpak AD-H; hexane/IPA, 95:5; 0.9 mL/min; λ = 220 nm): t_R = 23.7 (minor isomer) and 26.2 min (major isomer).

(3a*R*,8*R*,8a*S*)-8a-(Hydroxymethyl)-6-nitro-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (3i): White solid (47 mg, 77%); m.p. 129–131 °C. $[\alpha]_D^{22}$ = –71.0 (c = 1, CH_3OH); 90%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 1.2 Hz, 1

H), 6.72 (s, 1 H), 5.03 (dd, J = 6.8, 2.4 Hz, 1 H), 4.18 (dd, J = 12.4, 3.6 Hz, 1 H), 3.89 (s, 1 H), 3.63 (dd, J = 12.4, 8.8 Hz, 1 H), 2.88 (dd, J = 8.8, 3.6 Hz, 1 H), 2.31–2.22 (m, 1 H), 2.11–2.04 (m, 1 H), 2.01–1.92 (m, 1 H), 1.91–1.82 (m, 1 H), 1.80–1.70 (m, 1 H), 1.59–1.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 141.1, 135.6, 126.5 (q, $^1J_{C,F}$ = 282.0 Hz), 117.4, 99.7, 80.7 (q, $^2J_{C,F}$ = 30.0 Hz), 68.6, 66.8, 64.1, 32.2, 30.6 (q, $^3J_{C,F}$ = 3.0 Hz), 25.6 ppm. FTIR (neat): $\tilde{\nu}$ = 3138, 2959, 2367, 1503, 1289, 1173, 1090, 924, 747 cm^{-1}. HRMS: calcd. for $C_{12}H_{14}O_4N_2F_3$ [M + H]$^+$ 307.0906; found 307.0904. HPLC (Chiralpak AD-H; hexane/IPA, 90:10; 0.9 mL/min; λ = 254 nm): t_R = 11.4 (minor isomer) and 17.1 min (major isomer).

(3a*R*,8*S*,8a*R*)-5,6-Dibromo-8a-(hydroxymethyl)-8-(trifluoromethyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]pyrrolizin-8-ol (5a): White solid (46 mg, 55%); m.p. 133–135 °C. $[\alpha]_D^{22}$ = –78.9 (c = 1, CH_3OH); 90%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (s, 1 H), 4.94 (d, J = 5.6 Hz, 1 H), 4.16 (ddd, J = 9.2, 7.6, 1.2 Hz, 1 H), 4.08 (dd, J = 12.4, 7.6 Hz, 1 H), 3.88 (dd, J = 12.4, 6.4 Hz, 1 H), 3.69 (ddd, J = 12.8, 9.2, 5.2 Hz, 1 H), 2.95 (s, 1 H), 2.57–2.52 (m, 1 H), 2.33 (dd, J = 7.6, 6.8 Hz, 1 H), 2.30–2.23 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.8, 123.8 (q, $^1J_{C,F}$ = 282.0 Hz), 106.1, 102.6, 98.9, 97.4, 79.4 (q, $^2J_{C,F}$ = 30.0 Hz), 68.8, 66.9, 63.5, 32.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3441, 3222, 2964, 1436, 1284, 1162, 1050, 868, 796 cm^{-1}. HRMS: calcd. for $C_{11}H_{10}O_3NBr_2F_3$ [M]$^+$ 418.8980; found 418.8982. HPLC (Chiralpak AD-H; hexane/IPA, 95:5; 0.95 mL/min; λ = 220 nm): t_R = 22.1 (minor isomer) and 24.1 min (major isomer).

(3a*R*,8*S*,8a*R*)-6-Bromo-8a-(hydroxymethyl)-5-iodo-8-(trifluoromethyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]pyrrolizin-8-ol (5b): White solid (33 mg, 35%); m.p. 148–150 °C. $[\alpha]_D^{24}$ = –74.1 (c = 1, CH_3OH); 91%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 4.87 (dd, J = 6.0, 0.8 Hz, 1 H), 4.14 (ddd, J = 9.6, 8.0, 2.0 Hz, 1 H), 4.08 (dd, J = 12.4, 7.0 Hz, 1 H), 3.89 (dd, J = 12.4, 6.8 Hz, 1 H), 3.69 (ddd, J = 12.6, 9.2, 5.2 Hz, 1 H), 2.99 (s, 1 H), 2.58–2.53 (m, 1 H), 2.34 (t, J = 7.2 Hz, 1 H), 2.32–2.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 123.9 (q, $^1J_{C,F}$ = 282.0 Hz), 110.0, 106.8, 97.2, 79.6 (q, $^2J_{C,F}$ = 30.0 Hz), 68.8, 68.2, 68.0, 63.5, 32.8 ppm. FTIR (neat): $\tilde{\nu}$ = 3340, 2958, 1424, 1285, 1158, 1063, 944, 790 cm^{-1}. HRMS: calcd. for $C_{11}H_{10}O_3NBrF_3I$ [M]$^+$ 466.8841; found 466.8844. HPLC (Chiralcel OD-H; hexane/IPA, 90:10; 0.95 mL/min; λ = 220 nm): t_R = 9.3 (minor isomer) and 10.8 min (major isomer).

(3a*R*,8*S*,8a*R*)-5-Bromo-6-chloro-8a-(hydroxymethyl)-8-(trifluoromethyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]pyrrolizin-8-ol (5c): White solid (40 mg, 53%); m.p. 136–138 °C. $[\alpha]_D^{22}$ = –75.0 (c = 1, CH_3OH); 92%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (s, 1 H), 4.94 (d, J = 5.6 Hz, 1 H), 4.18–4.14 (m, 1 H), 4.08 (dd, J = 12.4, 7.2 Hz, 1 H), 3.88 (dd, J = 12.4, 6.8 Hz, 1 H), 3.69 (ddd, J = 12.8, 9.2, 5.2 Hz, 1 H), 3.00 (s, 1 H), 2.56–2.52 (m, 1 H), 2.35 (t, J = 7.2 Hz, 1 H), 2.31–2.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.8, 123.8 (q, $^1J_{C,F}$ = 282.0 Hz), 117.0, 103.8, 97.2, 96.4, 79.6 (q, $^2J_{C,F}$ = 30.0 Hz), 68.8, 66.8, 63.5, 32.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3450, 3246, 2951, 1407, 1285, 1173, 1045, 868, 794 cm^{-1}. HRMS: calcd. for $C_{11}H_{10}O_3NClBrF_3$ [M]$^+$ 374.9485; found 374.9486. HPLC (Chiralpak AD-H; hexane/IPA, 95:5; 0.9 mL/min; λ = 220 nm): t_R = 18.9 (minor isomer) and 20.8 min (major isomer).

(3a*R*,8*S*,8a*R*)-6-Chloro-8a-(hydroxymethyl)-5-iodo-8-(trifluoromethyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]pyrrolizin-8-ol (5d): White solid (37 mg, 44%); m.p. 147–149 °C. $[\alpha]_D^{22}$ = –63.1 (c = 1, CH_3OH); 90%*ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 4.87 (dd, J = 6.0, 0.8 Hz, 1 H), 4.14 (ddd, J = 9.2, 8.0, 2.0 Hz, 1 H), 4.08 (dd, J = 12.4, 7.2 Hz, 1 H), 3.89 (dd, J = 12.4, 6.8 Hz, 1 H), 3.69 (ddd, J = 13.0, 9.2, 5.2 Hz, 1 H), 3.06 (s, 1 H), 2.57–2.53 (m, 1 H), 2.37 (t, J = 7.2 Hz, 1 H), 2.32–2.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 123.9 (q, $^1J_{C,F}$ = 282.0 Hz), 123.5, 104.2, 97.0, 79.8 (q, $^2J_{C,F}$ = 30.0 Hz), 68.8, 67.9, 64.9, 63.5, 32.7 ppm. FTIR (neat): $\tilde{\nu}$ = 3446, 3247, 2958, 1733, 1401, 1284, 1172, 1039, 949, 868, 794 cm^{-1}. HRMS: calcd. for $C_{11}H_{10}O_3NClF_3I$ [M]$^+$ 422.9346; found 422.9348. HPLC (Chiralcel OJ-H; hexane/EtOH, 90:10; 0.9 mL/min; λ = 220 nm): t_R = 10.5 (minor isomer) and 13.2 min (major isomer).

General Procedure for the Chemoselective Suzuki Cross-Coupling Reaction: $Pd(PPh_3)_4$ (0.02 mmol) was added to a solution of **3b** (0.2 mmol) in 1,4-dioxane (2 mL) at room temp. under argon. The mixture was stirred at room temp. for 20 min, and then K_2CO_3 (0.4 mmol) in H_2O (1.3 mL) and phenylboronic acid (0.3 mmol) were added. The mixture was stirred at 80 °C for 4 h. The mixture was then cooled to room temp. and quenched by the addition of saturated $NaHCO_3$. The resulting solution was extracted with ethyl acetate. The organic layer was washed brine and dried with $MgSO_4$. Filtration of the organic layer and evaporation of the solvents gave the crude residue, which was purified by silica gel column chromatography to provide the 6-bromo-5-phenyl-substituted pyrrolizine-based triheterocycle **6a** as the desired coupling product. This general procedure was applied to **5b** to provide the desired coupling product **6b**.

(3a*R*,8*R*,8a*S*)-6-Bromo-8a-(hydroxymethyl)-5-phenyl-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (6a): White solid (62 mg, 74%); m.p. 146–148 °C. $[\alpha]_D^{22}$ = –38.8 (c = 1, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 2 H), 7.46–7.42 (m, 2 H), 7.38–7.34 (m, 1 H), 6.26 (s, 1 H), 5.25 (dd, J = 6.8, 3.6 Hz, 1 H), 4.12 (dd, J = 12.4, 3.6 Hz, 1 H), 3.56 (dd, J = 12.4, 9.6 Hz, 1 H), 3.46 (s, 1 H), 3.20 (dd, J = 9.6, 4.0 Hz, 1 H), 1.99–1.92 (m, 1 H), 1.81–1.73 (m, 1 H), 1.66–1.54 (m, 2 H), 1.53–1.47 (m, 1 H), 1.44–1.36 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4, 130.0, 128.8, 128.4, 127.8, 127.4, 124.8 (q, $^1J_{C,F}$ = 282.0 Hz), 105.0, 98.0, 80.1 (q, $^2J_{C,F}$ = 30.0 Hz), 65.4, 64.9, 64.3, 31.0, 30.3 (q, $^3J_{C,F}$ = 3.0 Hz), 25.0 ppm. FTIR (neat): $\tilde{\nu}$ = 3453, 3131, 2971, 1419, 1290, 1174, 1152, 1054, 1001, 945, 767 cm^{-1}. HRMS: calcd. for $C_{18}H_{17}O_2NBrF_3$ [M]$^+$ 415.0395; found 415.0396.

(3a*R*,8*S*,8a*R*)-6-Bromo-8a-(hydroxymethyl)-5-phenyl-8-(trifluoromethyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]pyrrolizin-8-ol (6b): White solid (67 mg, 80%); m.p. 143–145 °C. $[\alpha]_D^{23}$ = –52.9 (c = 1, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.45 (m, 4 H), 7.41–7.37 (m, 1 H), 6.34 (s, 1 H), 5.27 (d, J = 5.6 Hz, 1 H), 4.17 (dd, J = 12.4, 7.6 Hz, 1 H), 4.00–3.96 (m, 1 H), 3.88 (dd, J = 12.4, 6.4 Hz, 1 H), 3.47 (ddd, J = 13.0, 8.8, 5.2 Hz, 1 H), 2.87 (s, 1 H), 2.36 (dd, J = 7.6, 6.4 Hz, 1 H), 1.98–1.88 (m, 1 H), 1.68–1.63 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5, 129.6, 128.8, 128.7, 128.2, 127.4, 124.1 (q, $^1J_{C,F}$ = 282.0 Hz), 105.7, 99.2, 97.3, 78.6 (q, $^2J_{C,F}$ = 30.0 Hz), 68.6, 66.1, 63.5, 32.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3389, 2965, 1708, 1375, 1281, 1157, 1045, 946, 768 cm^{-1}. HRMS: calcd. for $C_{17}H_{15}O_3NBrF_3$ [M]$^+$ 417.0187; found 417.0185.

General Procedure for the Sequential 2nd Suzuki Cross-Coupling Reaction: $Pd(PPh_3)_4$ (0.02 mmol) was added to a solution of **6a** (0.2 mmol) in 1,4-dioxane (2 mL) at room temp. under argon. The mixture was stirred at room temp. for 20 min, and then K_2CO_3 (0.4 mmol) in H_2O (1.3 mL) and 4-methoxyphenylboronic acid (0.3 mmol) were added. The mixture was stirred at 100 °C for 6 h. The mixture was then cooled to room temp. and quenched by the addition of saturated $NaHCO_3$. The resulting solution was ex-

tracted with ethyl acetate. The organic layer was washed brine and dried with $MgSO_4$. Filtration of organic layer and evaporation of the solvents gave the crude residue, which was purified by silica gel column chromatography to provide the unsymmetrical 5,6-diaryl-substituted pyrrolizine-based triheterocycle **7a** as the desired coupling product. The general procedure was applied to **6b** to provide the desired coupling product **7b**.

(3a*R*,8*R*,8a*S*)-8a-(Hydroxymethyl)-6-(4-methoxyphenyl)-5-phenyl-8-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[*b*]pyrrolizin-8-ol (7a): White solid (80 mg, 90%); m.p. 76–78 °C. $[a]_D^{22}$ = +8.9 (*c* = 1, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 7.14–7.10 (m, 2 H), 6.77–6.74 (m, 2 H), 6.26 (s, 1 H), 5.23 (dd, *J* = 6.8, 3.6 Hz, 1 H), 4.12 (dd, *J* = 12.4, 4.0 Hz, 1 H), 3.76 (s, 3 H), 3.59 (dd, *J* = 12.4, 9.6 Hz, 1 H), 3.20 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.09 (s, 1 H), 2.06–1.99 (m, 1 H), 1.78–1.70 (m, 1 H), 1.64–1.58 (m, 2 H), 1.53–1.50 (m, 1 H), 1.42–1.33 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 132.6, 132.0, 129.5, 129.0, 128.6, 128.5, 127.2, 126.8, 126.1, 125.0 (q, $^1J_{C,F}$ = 282.0 Hz), 113.6, 101.9, 80.1 (q, $^2J_{C,F}$ = 30.0 Hz), 65.9, 64.6, 63.7, 55.1, 31.5, 30.5 (q, $^3J_{C,F}$ = 3.0 Hz), 25.2 ppm. FTIR (neat): $\tilde{\nu}$ = 3306, 2952, 1734, 1512, 1447, 1289, 1245, 1159, 1033, 946, 833, 797 cm^{-1}. HRMS: calcd. for $C_{25}H_{24}O_3NF_3$ $[M]^+$ 443.1708; found 443.1710.

(3a*R*,8*S*,8a*R*)-8a-(Hydroxymethyl)-6-(4-methoxyphenyl)-5-phenyl-8-(trifluoromethyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]pyrrolizin-8-ol (7b): White solid (83 mg, 93%); m.p. 50–52 °C. $[a]_D^{22}$ = –14.1 (*c* = 1, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 7.15–7.12 (m, 2 H), 6.78–6.75 (m, 2 H), 6.35 (s, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 4.19 (dd, *J* = 12.4, 8.0 Hz, 1 H), 4.00–3.95 (m, 1 H), 3.89 (dd, *J* = 12.4, 6.4 Hz, 1 H), 3.77 (s, 3 H), 3.56 (ddd, *J* = 12.6, 8.8, 4.8 Hz, 1 H), 2.84 (s, 1 H), 2.44 (dd, *J* = 7.6, 6.8 Hz, 1 H), 1.95–1.85 (m, 1 H), 1.65–1.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 132.7, 131.6, 129.4, 129.1, 128.8, 128.2, 127.8, 127.5, 125.9, 124.3 (q, $^1J_{C,F}$ = 282.0 Hz), 113.7, 102.5, 97.8, 78.4 (q, $^2J_{C,F}$ = 30.0 Hz), 68.6, 65.1, 63.7, 55.1, 32.5 ppm. FTIR (neat): $\tilde{\nu}$ = 3306, 2930, 1610, 1511, 1447, 1291, 1245, 1158, 1028, 835, 799 cm^{-1}. HRMS: calcd. for $C_{24}H_{22}O_4NF_3$ $[M]^+$ 445.1501; found 445.1504.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of all new compounds as well as chiral HPLC analysis data of **3a**–**3i** and **5a**–**5d**.

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[1] a) L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Acc. Chem. Res.* **2012**, *45*, 1278–1293; b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem.* **2011**, *123*, 6358–6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246; c) A. Padwa, *Chem. Soc. Rev.* **2009**, *38*, 3072–3081; d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; e) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.

[2] For selected reviews of asymmetric organocatalytic cascade reactions, see: a) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237–294; b) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320–332; *Angew. Chem. Int. Ed.* **2012**, *51*, 314–325; c) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 8642–8660; *Angew. Chem. Int. Ed.* **2011**, *50*, 8492–8509; d) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167–178; e) A.-N. Alba, X. Companyo, M. Viciano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432–1474; f) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; g) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.

[3] a) H.-J. Lee, C.-W. Cho, *J. Org. Chem.* **2013**, *78*, 3306–3312; b) J.-Y. Bae, H.-J. Lee, S.-H. Youn, S.-H. Kwon, C.-W. Cho, *Org. Lett.* **2010**, *12*, 4352–4355.

[4] a) G. J. Atwell, J.-Y. Fan, K. Tan, W. A. Denny, *J. Med. Chem.* **1998**, *41*, 4744–4754; b) I. Lalezari, E. L. Schwartz, *J. Med. Chem.* **1988**, *31*, 1427–1429.

[5] a) D. Ladurée, J.-C. Lancelot, M. Robba, E. Chenu, G. Mathé, *J. Med. Chem.* **1989**, *32*, 456–461; b) W. K. Anderson, H. L. McPherson Jr., *J. Med. Chem.* **1982**, *25*, 84–86.

[6] a) W. Liu, J. Zhou, K. Bensdorf, H. Zhang, H. Liu, Y. Wang, H. Qian, Y. Zhang, A. Wellner, G. Rubner, W. Huang, C. Guo, R. Gust, *Eur. J. Med. Chem.* **2011**, *46*, 907–913; b) S. E. Abbas, F. M. Awadallah, N. A. Ibrahim, A. M. Gouda, *Eur. J. Med. Chem.* **2010**, *45*, 482–491; c) A. J. Liedtke, P. R. W. E. F. Keck, F. Lehmann, A. Koeberle, O. Werz, S. A. Laufer, *J. Med. Chem.* **2009**, *52*, 4968–4972.

[7] For examples of asymmetric organocatalytic aza-Michael-participated cascade reactions with indoles or imidazoles as *N*-centered heteroaromatic nucleophiles, see: a) D. Enders, C. Joie, K. Deckers, *Chem. Eur. J.* **2013**, *19*, 10818–10821; b) D. Enders, A. Greb, K. Deckers, P. Selig, C. Merkens, *Chem. Eur. J.* **2012**, *18*, 10226–10229; c) H. Li, J. Zhao, L. Zeng, W. Hu, *J. Org. Chem.* **2011**, *76*, 8064–8069; d) L. Hong, W. Sun, C. Liu, L. Wang, R. Wang, *Chem. Eur. J.* **2010**, *16*, 440–444; e) D. Enders, C. Wang, G. Raabe, *Synthesis* **2009**, 4119–4124.

[8] For selected examples of asymmetric organocatalytic cascade aza-Michael–aldol reactions, see: a) M. Fernández, J. L. Vicario, E. Reyes, L. Carrillo, D. Badía, *Chem. Commun.* **2012**, *48*, 2092–2094; b) H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler, W. Wang, *Org. Lett.* **2007**, *9*, 965–968; c) H. Sundén, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 827–832.

[9] a) A. Studer, *Angew. Chem.* **2012**, *124*, 9082–9090; *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958; b) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455–529; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; d) H. L. Yale, *J. Med. Chem.* **1959**, *2*, 121–133.

[10] S.-J. Lee, S.-H. Youn, C.-W. Cho, *Org. Biomol. Chem.* **2011**, *9*, 7734–7741.

[11] For recent reviews of asymmetric organocatalytic aza-Michael reactions, see: a) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan, F. Y. Kwong, *ChemCatChem* **2012**, *4*, 917–925; b) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058–11076.

[12] Under the optimized reaction conditions, the cascade reaction did not proceed with cyclohex-1-enecarbaldehyde.

[13] a) H.-J. Lee, C.-W. Cho, *Bull. Korean Chem. Soc.* **2011**, *32*, 359–362; b) M. D. Morrison, J. J. Hanthorn, D. A. Pratt, *Org. Lett.* **2009**, *11*, 1051–1054; c) J. A. Smith, S. Ng, J. White, *Org. Biomol. Chem.* **2006**, *4*, 2477–2482.

[14] a) R. G. Berlinck, M. H. Kosuga, *Nat. Prod. Rep.* **2005**, *22*, 516–550; b) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–49; c) E. Hao, J. Fromont, D. Jardine, P. Karuso, *Molecules* **2001**, *6*, 130–141; d) G. W. Gribble, *J. Nat. Prod.* **1992**, *55*, 1353–1395.

[15] CCDC-954155 (for **3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] For iminium activation in organocatalysis, see: a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; b) G. Lelais, D. W. C. MacMillan, *Aldrichim. Acta* **2006**, *39*, 79–87; c) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.

[17] For the first development of diarylprolinol silyl ethers as organocatalysts, see: a) M. Marigo, T. C. Wabnitz, D. Fielenbach,

K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

[18] a) W. J. Peláez, M. A. Burgos Paci, G. A. Argüello, *Tetrahedron Lett.* **2009**, *50*, 1934–1938; b) J. J. Richards, T. E. Ballard, R. W. Huigens III, C. Melander, *ChemBioChem* **2008**, *9*, 1267–1279; c) R. Kumar, J. W. Lown, *Org. Biomol. Chem.* **2003**, *1*, 3327–3342.

[19] F. Huang, Z.-K. Yao, Y. Wang, Y. Wang, J. Zhang, Z.-X. Yu, *Chem. Asian J.* **2010**, *5*, 1555–1559.

[20] L. A. Paquette, M. M. Schulze, D. G. Bolin, *J. Org. Chem.* **1994**, *59*, 2043–2051.

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