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Cu(I)/TF-BiphamPhos-Catalyzed Asymmetric Michael Addition of Cyclic Ketimino Esters to Alkylidene Malonates

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Cu(I)-Catalyzed asymmetric Michael addition of cyclic ketimino esters with alkylidene malonates has been developed for efficient construction of β-branched α-amino acids containing adjacent quaternary and tertiary stereogenic centers in good yields with excellent diastereo-/enantioselectivities. The generated Michael adduct was further converted to the biologically important pyrrolizidine analogues via one-pot sequential reduction/lactamization.

Introduction

The fused pyrrolizidine moiety is the key structure of a great deal of natural products and biologically active molecules,[1] and some typical examples are exhibited in Figure 1. Penibruguieramine (**A**), a pyrrolizidinone alkaloid isolated from the Chinese mangrove *Bruguiera gymnorrhiza*, exhibits potent antibacterial activity against *Staphylococcus aureus*.[2] Pyrrolizidine (**B**) is a highly effective phosphodiesterase IVb inhibitor for the treatment of respiratory disorders such as asthma and chronic obstructive pulmonary disease.[3] Pyrrolizidine (**C**), a new scaffold for human NK1 antagonist, has wonderful potency and serviceable duration of action for central antagonist activity in the gerbil model.[4] Due to the wide application of pyrrolizidine derivatives in medicinal chemistry, a variety of strategies have been reported to obtain this type of compounds in the past decades.[5] However, there are still some disadvantages to the previously reported approaches, such as relatively long synthetic steps and low yields. Therefore, the development of a simple and easily-handled synthetic route for pyrrolizidine analogues are highly desirable.

Acyclic imino esters derived from glycinate, as the activated α-amino acid fragments, has been successfully employed in many asymmetric transformations, such as asymmetric 1,3-dipolar cycloaddition,[6] Michael addition,[7] alkylation,[8] and Mannich reactions.[9] On the contrary, less reactive cyclic ketone-derived imino esters have been seldom utilized in asymmetric reaction due to the steric hindrance. Recently, Park developed an asymmetric alkylation of readily-available cyclic imino esters

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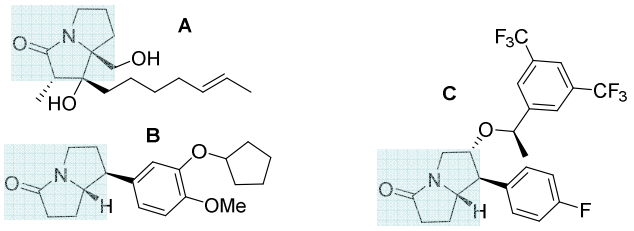
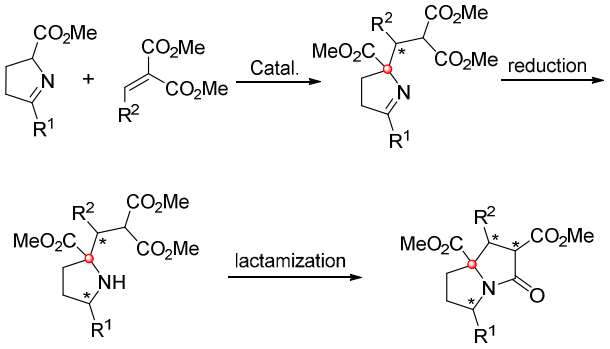


Figure 1. Examples of bioactive molecules containing pyrrolizidine motif.

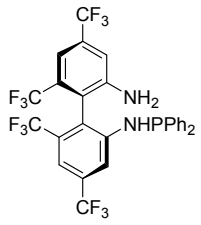
with the chiral quaternary ammonium catalysts, affording the quaternary α-amino acid derivatives with good yields and high enantioselectivities.[10] Most recently, we disclosed that cyclic imino esters could be used as efficient precursors of azomethine ylides in Ag(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition reaction affording the bioactive azabicyclo[2.2.1]heptanes.[11] Based on our previous efforts on azomethine ylide-involved catalytic asymmetric



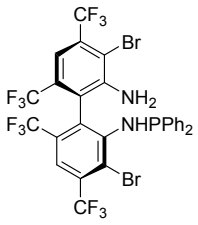
Scheme 1. Proposed Michael addition of cyclic ketimino esters to alkylidene malonates followed by seqential reduction/lactamization for the construction of chiral pyrrolizidine analogues.

1,3-dipolar cycloaddition[12] and Michael addition reaction,[13] we envisioned that the enantioenriched heterocyclic pyrrolizidine analogues could be achieved through metal-catalyzed asymmetric Michael addition of cyclic azomethine ylides to alkylidene malonates, then followed by sequential simple reduction/lactamization process (Scheme 1). The concomitant challenge of the designed transformation is the stereoselectivity control of up to four generated stereogenic centers. In this article, we report our preliminary results.

Table 1. Optimization for the catalytic asymmetric Michael addition of cyclic imino ester **1a** with alkylidene malonates **2a**[a]



(*S*)-TF-BiphamPhos **L1**



(*S*)-TF-BiphamPhos **L2**

1a **3a** (> 19:1 dr)

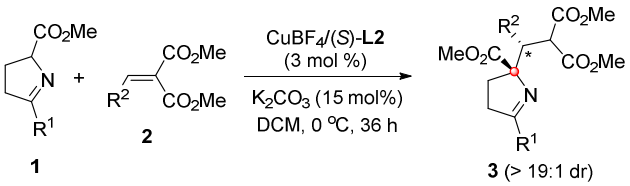
Entry	L	[M]	Solvent	Base	Yield[b] (%)	Ee[c,d] (%)
1	**L1**	AgOAc	DCM	K_2CO_3	75	50
2	**L1**	$CuBF_4$	DCM	K_2CO_3	80	64
3	**L2**	$CuBF_4$	DCM	K_2CO_3	82	94
4	**L2**	$CuBF_4$	$CHCl_3$	K_2CO_3	79	93
5	**L2**	$CuBF_4$	MeCN	K_2CO_3	75	77
6	**L2**	$CuBF_4$	THF	K_2CO_3	69	75
7	**L2**	$CuBF_4$	EtOAc	K_2CO_3	74	86
8	**L2**	$CuBF_4$	PhMe	K_2CO_3	69	93
9	**L2**	$CuBF_4$	Et_2O	K_2CO_3	77	93
10	**L2**	$CuBF_4$	DCM	TEA	65	94
11	**L2**	$CuBF_4$	DCM	$^iPr_2NH$	66	91
12	**L2**	$CuBF_4$	DCM	$CsCO_3$	80	88
13[e]	**L2**	$CuBF_4$	DCM	K_2CO_3	81	97
14[f]	**L2**	$CuBF_4$	DCM	K_2CO_3	70	97

[a] All reactions were carried out with 0.23 mmol of **1a** and 0.35 mmol of **2a** in 2 mL of solvent. $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b] Isolated yield. [c] Determined by the crude ^1H NMR. [d] Determined by HPLC analysis. [e] At 0 °C. [f] At -20 °C.

Results and discussion

Initially, we investigated the Michael addition of cyclic imino ester **1a** with alkylidene malonate **2a** using AgOAc/TF-BiphamPhos **L1** (3 mol %) in the presence of K_2CO_3 (15 mol %) in 2 mL CH_2Cl_2 at room temperature. To our delight, the reaction proceeded smoothly

Table 2. Substrate scope of Cu(I)/**L2**-catalyzed asymmetric Michael addition of cyclic imino ester **1** with alkylidene malonates **2**[a]



1 **2** **3** (> 19:1 dr)

Entry	R^1	R^2	Yield[b] (%)	3	Ee[c,d] (%)
1	*p*-Cl-C_6H_4 (**1a**)	Ph (**2a**)	81	**3a**	97
2	*p*-Cl-C_6H_4 (**1a**)	*p*-Cl-C_6H_4 (**2b**)	85	**3b**	96
3	*p*-Cl-C_6H_4 (**1a**)	*m*-Cl-C_6H_4 (**2c**)	78	**3c**	93
4	*p*-Cl-C_6H_4 (**1a**)	*o*-F-C_6H_4 (**2d**)	76	**3d**	96
5	*p*-Cl-C_6H_4 (**1a**)	*p*-Br-C_6H_4 (**2e**)	86	**3e**	92
6	*p*-Cl-C_6H_4 (**1a**)	*p*-F-C_6H_4 (**2f**)	87	**3f**	93
7	*p*-Cl-C_6H_4 (**1a**)	*p*-CF_3-C_6H_4 (**2g**)	83	**3g**	94
8	*p*-Cl-C_6H_4 (**1a**)	*p*-Me-C_6H_4 (**2h**)	89	**3h**	98
9[e]	*p*-Cl-C_6H_4 (**1a**)	*p*-MeO-C_6H_4 (**2i**)	81	**3i**	97
10[f]	*p*-Cl-C_6H_4 (**1a**)	2-furyl (**2j**)	88	**3j**	88
11	*p*-Cl-C_6H_4 (**1a**)	*n*-Pr (**2k**)	71	**3k**	91
12	*p*-Me-C_6H_4 (**1b**)	Ph (**2a**)	86	**3l**	97
13	*p*-MeO-C_6H_4 (**1c**)	Ph (**2a**)	82	**3m**	99
14	*p*-CF_3-C_6H_4 (**1d**)	Ph (**2a**)	87	**3n**	97

[a] All reactions were carried out with 0.23 mmol of **1** and 0.35 mmol of **2** in 2 mL of DCM. [b] Isolated yield. [c] Determined by the crude ^1H NMR. [d] Determined by HPLC analysis. [e] dr = 7:1. [f] dr = 7:1

to provide the desired Michael adduct **3a** in 75% yield with excellent diastereoselectivity (>19:1 dr) albeit with only moderate enantioselectivity (Table 1, entry 1). The enantioselectivity was improved from 50% to 74%, when $Cu(CH_3CN)_4BF_4$ was employed as metal precursor in this transformation (entry 2). Using (*S*)-TF-BiphamPhos (**L2**) bearing two bromines at the 3,3'-position as chiral ligand, the adduct **3a** was obtained in good yield (82%) with excellent diastereoselectivity (> 19:1) and significantly enhanced enantioselectivity (94% ee) (entry 3). To further improve the enantioselectivity of this reaction, several solvents were also probed, and it was found that CH_2Cl_2 led to the best result in terms of both yields and enantioselectivities (entries 4-9). Subsequently, the effect of bases was also studied, and K_2CO_3 (15 mol%) was the optimal base in this transformation (entries 3 and 10-12). The enantioselectivity could be further increased to 97% when the reaction temperature was decreased from room temperature to 0 °C (entry 13).

Next, under the optimized reaction conditions (3 mol% Cu(I)/(*S*)-**L2** and 15 mol % K_2CO_3 in CH_2Cl_2 at 0 °C), the asymmetric Michael addition reaction of cyclic imino ester **1a** as a Michael donor with a wide variety of alkylidene malonates **2** derived from various aromatic aldehydes were investigated to test the generality of this methodology. As shown in Table 2, all reactions proceeded smoothly to afford the expected adducts **3a-3j** in 76-89 % yields with 88-98% ee and 7:1-> 19:1 dr (Table 2, entries 1–10). Those

results indicated that stereoselectivity and the rate of the reaction were not affected by the electronic effects and the substituent patterns of the phenyl rings of alkylidene malonates. It is noteworthy that heteroaryl substituted alkylidene malonates **2j** also worked well in this transformation giving the corresponding addition product **3j** in 88% yield with 7:1 dr and 88% ee (entry 10). Remarkable, alkyl substituted alkylidene malonate (**2k**) was also tolerated in this catalytic system affording the desired addition product in good yield with exclusive diastereoselectivity (>19:1 dr) and high enantioselectivity (91% ee) (entry 11). The generality of Michael donors was further explored under the optimized reaction conditions. In general, various cyclic aryl substituted imino esters bearing electron-deficient or electron-rich groups were all tolerated in this reaction, providing the desired Michael adducts in good yields (82-89%) with excellent enantioselectivities (97-99%) (entries 12-14). No reaction occurred when the cyclic imino ester with methyl substitution was employed in this transformation.

The enantioenriched adduct **3a** containing contiguous stereogenic centers could be easily elaborated into biologically important and synthetically useful pyrrolizidine analogues containing four stereogenic centers (Scheme 2). Treatment the adduct **3a** with BH_3/Me_2S followed by lactamization in one-pot process gave rise to the corresponding pyrrolizidine **4** with two additional stereogenic centers in 90% yield with >19:1 dr and 97% ee. Notably, excellent diastereoselectivity control was observed for both reduction and lactamization steps. The relative and absolute configuration of pyrrolizidine **4** was unequivocally determined to be (1*S*,2*R*,5*S*,7a*R*) by X-ray diffraction analysis (Figure 2).

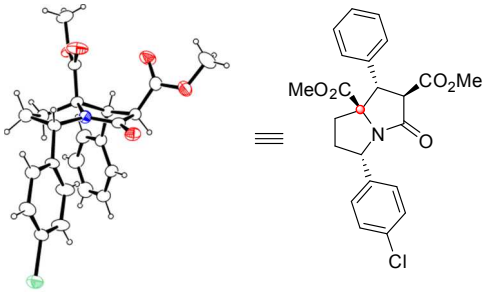


Figure 2. X-ray structure of (1*S*,2*R*,5*S*,7a*R*)-**4**

Conclusions

In conclusion, we have successfully developed an efficient Cu(I)-catalyzed asymmetric Michael addition of cyclic azomethine ylides with alkylidene malonates to construct the β-branched α-amino acids bearing adjacent quaternary and tertiary stereogenic centers. It was found that the catalytic system was very effective in this transformation, and good yields (71-89%), good to high diastereoselectivities (> 19:1 dr) and excellent enantioselectivities (88-99% ee) were obtained for various cyclic azomethine ylides and alkylidene malonates. The synthetic potential of this methodology has been demonstrated by facile transformation of the obtained β-branched α-amino acid into biologically important pyrrolizidine analogues via sequential reduction/lactamization. Further investigations on the application of this method in organic synthesis and additional studies focused on the scope and limitations of this reaction are in progress.

Experimental section

General

^{1}H NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer in chloroform-d3. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, brs = broad singlet, coupling constant (s) in Hz, integration). ^{13}C NMR spectra were recorded on a VARIAN Mercury 75 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Diastereomeric ratios were determined from crude ^{1}H NMR. Enantiomeric ratios were determined by HPLC, using a chiralcel IC-H column, a chiralcel AD-H column with hexane and *i*-PrOH as solvents. The absolute configuration of the product **4** was determined as (1*S*,2*R*,5*S*,7a*R*) by X-ray diffraction analysis. Cyclic ketimino esters, alkylidene malonates and chiral Ligand **L1** and **L2** were prepared according to the literature procedure.[12t]

General procedure for asymmetric Michael addition of the cyclic ketimino esters with alkylidene malonates catalyzed by Cu(I)/-TF-BiphamPhos Complexes

Under argon atmosphere (*S*)-TF-BiphamPhos **L2**（6.0 mg, 0.0075 mmol) and $Cu(CH_3CN)_4BF_4$ (1.2 mg, 0.007 mmol) were dissolved in 2 mL DCM, and stirred at room temperature for about 1 h. Then, the cyclic ketimino esters **1** (0.23 mmol), K_2CO_3 (0.04 mmol) and alkylidene malonates **2** (0.35 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The crude product was analyzed by ^{1}H NMR to determine the diastereoselectivity, and then the residue was purified by column chromatography to give the corresponding Michael product **3**, which was then directly analyzed by chiral HPLC to determine the enantiomeric excess.

Dimethyl 2-((*S*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(phenyl)methyl)malonate 3a.The title compound was prepared according to the general procedure as described above in 81% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +121.5 (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.15 (s, 5H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.31 (s, 3H), 2.72-2.67 (m, 1H), 2.37-2.27 (m, 1H), 2.22-2.12 (m, 1H), 2.09-1.98 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.67, 35.09, 51.14, 52.07, 52.29, 52.61, 54.11, 85.54, 127.32, 127.79, 128.55, 129.40, 129.80, 132.00, 136.86, 167.94, 168.48, 173.50, 175.13; HRMS calcd. for $C_{24}H_{24}ClNO_6$+H^+: 458.1365, found 458.1361. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 97% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 6.94 and 13.62 min.

Dimethyl 2-((*S*)-(4-chlorophenyl)((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)malonate 3b. The title compound was prepared according to the general procedure as described above in 85% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +124.7 (*c* 1.72, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 3.6Hz, 4H), 4.46 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.36 (s, 3H), 2.77-2.74 (m, 1H), 2.34-2.20 (m, 1H), 2.19-2.10 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.35, 35.23, 50.48, 52.30, 52.44, 52.75, 54.08, 85.46, 128.08, 128.70, 129.46, 131.18, 131.86, 133.43, 135.65, 137.34, 167.88, 168.31, 173.29, 175.40. HRMS calcd. for $C_{24}H_{23}Cl_2NO_6$+H^+: 492.0975, found 492.0968. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 96% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.45 and 23.68 min.

Dimethyl 2-((*S*)-(3-chlorophenyl)((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)malonate 3c. The title compound was prepared according to the general procedure as described above in 78% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +122.8 (*c* 1.76, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = Hz, 2H), 7.19-7.13 (m, 2H),7.10-7.04 (m, 2H), 4.47 (d, *J* = 10.5 Hz, 1H), 4.38 (d, *J* = 10.5 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 1H), 3.37 (s, 3H), 2.82-2.75 (m, 1H), 2.38-2.31 (m, 1H), 2.24-2.12 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75MHz) δ 30.23, 35.19, 50.66, 52.20, 52.25, 52.67, 53.89, 85.39, 127.53, 127.84, 128.58, 129.03, 129.39, 130.01, 131.76, 133.63, 137.21, 139.13, 167.72, 168.15, 173.06, 175.40. HRMS calcd. for $C_{24}H_{23}Cl_2NO_6$+H^+: 492.0975, found 492.0966. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 93% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.23 and 11.53 min.

Dimethyl 2-((*S*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(2-fluorophenyl)methyl)malonate 3d. The title compound was prepared according to the general procedure as described above in 76% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +156.8 (*c* 2.19, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300MHz) δ 7.79 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.20-7.14 (m, 1H), 7.05-6.99 (m, 2H), 6.86-6.81 (m, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.36 (s, 3H), 2.77-2.68 (m, 1H), 2.37-2.28 (m, 1H), 2.17-2.12 (m, 1H), 2.08-1.99 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75MHz) δ 30.75, 35.17, 43.14, 52.25, 52.44, 52.75, 53.70, 85.06, 115.26 (d, $J_{C\text{-}F}$ = 23.1 Hz), 123.40, 124.49 (d, $J_{C\text{-}F}$ = 13.8 Hz), 128.64, 129.13 (d, $J_{C\text{-}F}$ = 8.4 Hz), 129.47, 130.40, 131.96, 137.20, 160.97 (d, $J_{C\text{-}F}$ = 245.3 Hz), 167.93, 168.33, 173.52, 175.26. HRMS calcd. for $C_{24}H_{23}ClFNO_6$+H^+: 476.1271, found 476.1264. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 96% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.44 and 10.35 min.

Dimethyl 2-((*S*)-(4-bromophenyl)((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)malonate 3e. The title compound was prepared according to the general procedure as described above in 86% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +134.6 (*c* 1.66, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.31-7.27 (m, 2H), 7.05 (d, *J* = 8.1Hz 2H), 4.45 (d, *J* = 10.5 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.36 (s, 3H), 2.81-2.72 (m, 1H), 2.37-2.29 (m, 1H), 2.25-2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.32, 35.21, 50.48, 52.27, 52.41, 52.71, 53.99, 85.36, 121.59, 128.66, 129.43, 131.00, 131.49, 131.82, 136.17, 137.30, 167.82, 168.24, 173.21,175.30. HRMS calcd. for $C_{24}H_{23}BrClNO_6$+H^+: 536.0470, found 536.0461. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 92% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.97 and 25.87 min.

Dimethyl 2-((*S*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(4-fluorophenyl)methyl)malonate 3f. The title compound was prepared according to the general procedure as described above in 87% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +130.4 (*c* 1.38, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.17-7.12 (m, 2H), 6.89-6.83 (m, 2H), 4.46 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 10.5 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.34 (s, 3H), 2.79-2.72 (m, 1H), 2.37-2.30 (m, 1H), 2.17-2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.35, 35.17, 50.41, 52.21, 52.39, 52.71, 54.19, 85.56, 114.80 (d, $J_{C\text{-}F}$ = 21.1 Hz), 128.67, 129.44, 131.48 (d, $J_{C\text{-}F}$ = 7.7 Hz), 131.90, 132.76, 137.28, 161.92 (d, $J_{C\text{-}F}$ = 245.1 Hz), 167.92, 168.36, 173.37, 175.23. HRMS calcd. for $C_{24}H_{23}ClFNO_6$+H^+: 476.1271, found 476.1265. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 93% ee, determined by HPLC (Chiralcel IC, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 8.39, 8.90, 9.88 and 13.02 min.

Dimethyl 2-((*S*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(4-(trifluoromethyl)phenyl)methyl) malonate 3g. The title compound was prepared according to the general procedure as described above in 83% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +116.6 (*c* 1.47, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.46-7.26 (m, 6H), 4.58 (d, *J* = 10.5 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.34 (s, 3H), 2.85-2.74 (m, 1H), 2.40-2.31 (m, 1H), 2.27-2.17 (m, 1H), 2.13-2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.38, 35.28, 50.763, 52.33, 52.52, 52.82, 54.08, 85.39, 123.87 (q, $J_{C\text{-}F}$ = 271.0 Hz), 124.82, 128.77, 129.48, 130.27, 131.82, 137.48, 141.54, 167.83, 168.22, 173.09, 175.47. HRMS calcd. for $C_{25}H_{23}ClF_3NO_6$+H^+: 526.1239, found 526.1230. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 94% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 6.05 and 20.78 min.

Dimethyl 2-((*S*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(p-tolyl)methyl)malonate 3h. The title compound was prepared according to the general procedure as described above in 89% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = 140.5 (*c* 0.34, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.03(d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.5 Hz, 2H), 4.44 (d, *J* = 10.8 Hz 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.33 (s, 3H), 2.76-2.68 (m, 1H), 2.34-2.27 (m, 1H), 2.24 (s, 3H), 2.19-2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 20.98, 30.33, 35.21, 50.80, 52.16, 52.34, 52.66, 54.24, 85.78, 106.21, 128.60, 129.48, 129.66, 132.14, 133.80, 137.00, 168.09, 168.61, 173.65, 175.10. HRMS calcd. for $C_{25}H_{26}ClNO_6$+H^+: 472.1521, found 472.1512. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 98% ee, determined by HPLC

(Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 6.46 and 14.59 min.

Dimethyl 2-((*S*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(4-methoxyphenyl)methyl)malonate 3i. The title compound was prepared according to the general procedure as described above in 81% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +562.8 (*c* 0.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.69-6.67 (d, *J* = 8.4 Hz, 2H), 4.39 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 3.67(s, 3H), 3.34 (s, 3H), 2.76-2.67 (m, 1H), 2.36-2.27 (m, 1H), 2.20-2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.45, 35.20, 50.53, 52.20, 52.67, 54.31, 55.04, 85.81, 113.24, 128.05, 128.64, 129.49, 130.37, 130.99, 137.l6, 168.11, 168.61, 173.76, 175.12. HRMS calcd. for $C_{25}H_{26}ClNO_7$+H^+: 488.1471, found 488.1462. The product was analyzed to determine the diastereoselectivity of the reaction: 7:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 97% ee, determined by HPLC (Chiralcel IC, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 14.31, 18.66, 22.27 and 23.55 min.

Dimethyl 2-((*R*)-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl)-3,4-dihydro-2H-pyrrol-2-yl)(furan-2-yl)methyl)malonate 3j. The title compound was prepared according to the general procedure as described above in 88% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +111.3 (*c* 1.46, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 6.23 (s, 1H), 6.07 (d, *J* = 3.0 Hz, 1H), 4.81 (d, *J* = 10.2 Hz, 1H), 4.09 (d, *J* = 9.9 Hz, 1H), 3.73 (s, 3H), 3.61 (s, 3H), 3.50 (s, 3H), 2.98-2.87 (m, 1H), 2.61-2.50 (m, 1H), 2.45-2.35 (m, 1H), 2.30-2.20 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 29.39, 35.47, 44.78, 46.55, 52.47, 52.63, 85.73, 108.94, 110.44, 128.58, 129.31, 129.51, 132.04, 137.21, 141.93,151.34, 167.84, 167.99, 172.87, 175.36. HRMS calcd. for $C_{22}H_{22}ClNO_7$+H^+: 448.1158, found 448.1153. The product was analyzed to determine the diastereoselectivity of the reaction: 7:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 88% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.53, 9.23, 13.15 and 15.29 min.

Dimethyl 2-((*R*)-1-((*R*)-5-(4-chlorophenyl)-2-(methoxycarbonyl) 3,4-dihydro-2H-pyrrol-2-yl)butyl)malonate 3k. The title compound was prepared according to the general procedure as described above in 71% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +83.9 (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.64 (s, 1H), 3.61-3.57 (m, 1H), 3.50 (d, *J* = 5.4 Hz, 1H), 3.09-3.00 (m, 2H), 2.69-2.60 (m, 1H), 2.01-1.90 (m, 1H), 1.58-1.52 (m, 1H), 1.42-1.26 (m, 3H), 0.94-0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 14.42, 21.33, 27.13, 30.82, 35.87, 43.82, 51.84, 52.17, 52.44, 52.61, 87.34, 128.63, 129.45, 132.15, 137.24, 169.33, 169.61, 173.49, 174.53. HRMS calcd. for $C_{21}H_{26}ClNO_6$+H^+: 424.1521, found 424.1517. The product was analyzed to determine the diastereoselectivity of the reaction: 19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 91% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 5.53, 8.12, 8.97 and 13.52 min.

Dimethyl 2-((*S*)-((*R*)-2-(methoxycarbonyl)-5-(p-tolyl)-3,4-dihydro-2H-pyrrol-2-yl)(phenyl)methyl)malonate 3l. The title compound was prepared according to the general procedure as described above in 86% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +75.60 (*c* 0.58, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.22-7.17 (m, 7H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* =10.8 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.307 (s, 3H), 2.79-2.72 (m, 1H), 2.40 (s, 3H), 2.33-2.30 (m, 1H), 2.21-2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.48, 30.11, 35.26, 51.19, 52.14, 52.31, 52.69, 54.28, 85.660 127.32, 127.87, 128.19, 129.05, 129.90, 131.02, 137.22, 141.34, 168.17, 168.62, 173.76, 176.17. HRMS calcd. for $C_{25}H_{27}NO_6$+H^+: 438.1911, found 438.1905. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 97% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.18 and 17.72 min.

Dimethyl 2-((*S*)-((*R*)-2-(methoxycarbonyl)-5-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrol-2-yl)(phenyl)methyl)malonate 3m. The title compound was prepared according to the general procedure as described above in 82% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +32.5 (*c* 0.71, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.81 (d, *J* = 8.7 Hz, 2H), 7.16 (s, 4H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.40 (d, *J* =10.8 Hz, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.31 (s, 3H), 2.78-2.71 (m, 1H), 2.36-2.26 (m, 1H), 2.20-2.09 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.05, 35.15, 51.17, 52.11, 52.26, 52.65, 54.23, 55.27, 85.56, 113.60, 126.49, 127.28, 127.83, 129.87, 137.21, 168.15, 168.59, 173.78, 175.51. HRMS calcd. for $C_{25}H_{27}NO_7$+H^+: 454.1860, found 454.1859. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 99% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 9.87 and 19.09 min.

Dimethyl 2-((*S*)-((*R*)-2-(methoxycarbonyl)-5-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyrrol-2-yl)(phenyl)methyl)malonate 3n. The title compound was prepared according to the general procedure as described above in 87% yield. It was purified by flash chromatography to afford white solid. $[\alpha]^{25}_D$ = +65.5 (*c* 0.59, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.16 (m, 4H), 4.46 (s, 2H), 3.72 (s, 3H), 3.31 (s, 3H), 3.65 (s, 3H), 2.77-2.69 (m, 1H), 2.34-2.29 (m, 1H), 2.21-2.15 (m, 1H), 2.10-2.02 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.63, 35.33, 51.28, 52.23, 52.49, 52.77, 54.25, 85.76, 123.88 (q, J_{C-F} = 265.6 Hz), 125.42, 127.52, 127.97, 128.49, 129.96, 136.89, 168.06, 168.62, 173.55, 175.25. HRMS calcd. for $C_{25}H_{24}FNO_6$+H^+: 492.1634, found 492.1630. The product was analyzed to determine the diastereoselectivity of the reaction: >19:1 dr, determined by ^{1}H NMR, and the enantioselectivity: 97% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm); t_r = 7.76 and 10.98 min.

Synthetic transformation of the Michael adduct 3a

Dimethyl (1*S*,2*R*,5*S*,7a*R*)-5-(4-chlorophenyl)-3-oxo-1-phenyltetrahydro-1H-pyrrolizine-2,7a(5H)-dicarboxylate 4. A solution of 2 M BH_3 in Me_2S (0.4 mL) was added dropwise to a stirred solution of Michael adduct **3a** (0.4 mmol) in 5 mL DCM. The mixture was stirred at room temperature for 3 h. The residue was first evaporated at reduced pressure, then the crude mixture was treated with 5 mL MeOH and TFA (0.8 mmol). The resulting mixture stirred at 50 °C for 12h. Once starting material was consumed (monitored by TLC), the residue was evaporated at reduced pressure. The crude product was analyzed by ^{1}H NMR to determine the diastereoselectivity (> 19:1 dr), and then the residue was purified by column chromatography (PE : EA = 3:1) to give the corresponding pyrrolizidine **4** as a white solid in 90% yield. $[\alpha]^{25}_D$ = +131.2 (*c* 1.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.44-7.39 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.71 (d, *J* = 9.3 Hz, 1H), 4.39 (s, 1H), 3.89 (s, 3H), 3.78 (s, 1H), 3.74 (s, 3H), 2.58-2.51 (m, 1H), 1.87-1.80 (m, 2H), 1.39-1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 30.61,

36.15, 47.52, 52.92, 53.11, 56.36, 53.11, 56.36, 58.94, 78.56, 128.02, 128.20, 128.45, 128.71, 128.98, 133.46, 138.03, 138,29, 164.43, 168.75, 174.29. HRMS calcd. for $C_{23}H_{22}ClNO_5$+H^+: 428.1259, found 428.1255. The product was analyzed to determine the enantioselectivity: 97% ee, determined by HPLC (Chiralcel AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 9.57 and 11.35 min.

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