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Nucleophilic Phosphine-Catalyzed Intramolecular Michael Reactions of *N*-Allylic Substituted α-Amino Nitriles: Construction of Functionalized Pyrrolidine Rings via 5-*endo*-trig Cyclizations

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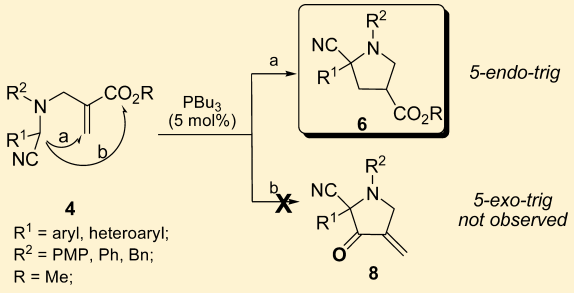
Supporting Information

ABSTRACT: Pyrrolidine rings are common moieties for pharmaceutical candidates and natural compounds, and the construction of these skeletons has received much attention. α-Amino nitriles are versatile intermediates in synthetic chemistry and have been widely used in the generation of multiple polyfunctional structures. Herein, a novel nucleophilic phosphine-catalyzed intramolecular Michael reaction of *N*-allylic substituted α-amino nitriles has been developed for the efficient construction of functionalized 2,4-disubstituted pyrrolidines (*N*-heterocyclic α-amino nitriles) via 5-*endo*-trig cyclization. Furthermore, the one-pot sequence of the synthesis of pyrrolidine and the subsequent transformations of the functionalized products have also been demonstrated.



INTRODUCTION

Five-membered nitrogen-atom-containing heterocycles constitute one of the most important classes of heterocyclic compounds in the pharmaceutical and agrochemical industries.[1] In particular, pyrrolidine rings have received considerable attention from the synthetic community due to their frequent occurrence in nature and wider relevance to numerous biologically active natural products and pharmacologically relevant therapeutic agents.[2] A variety of synthetic methods have been developed to construct these structurally useful motifs.[3] As a straightforward strategy to access these nitrogen incorporated heterocycles, intramolecular cyclization pathways have thus gained much interest.[4] However, the construction of pyrrolidine rings via intramolecular catalytic nucleophile-driven 5-*endo*-trig cyclization, which is a geometrically disfavored process according to Baldwin's rules, is rare, despite the fact that the syntheses of such saturated five-membered nitrogen heterocycles via metal-catalyzed intramolecular 5-*endo*-trig cyclizations have been studied extensively in recent years.[5] Within this context, the development of catalytic intramolecular nucleophile-driven cyclization via a 5-*endo*-trig mode to access pyrrolidine rings still represents a synthetic challenge and is highly demanded.

α-Amino nitriles bearing an α-hydrogen are exceptionally versatile intermediates in synthetic chemistry and have been widely used in the generation of multiple polyfunctional structures due to the powerful anion-stabilizing capacity of the cyano group.[6] Recently, Opatz et al. have reported that addition of deprotonated α-amino nitriles by stoichiometric strong base to α,β-unsaturated carbonyl compounds, followed by subsequent reductive decyanation, resulted in polysubstituted pyrrolidines in a one-pot reaction sequence.[7] Very recently, we have developed an efficient tertiary amine-catalyzed multicomponent tandem reaction to prepare funcationalized α-amino nitriles and α-methylene-γ-butyrolactams via 5-*exo*-trig cyclization.[8a−c] However, the development of a metal-free catalytic process to construct functionalized pyrrolidine rings from α-amino nitriles under mild reaction conditions is unexploited. Nucleophilic phosphine catalysis has advanced rapidly as a powerful tool for assembling the diverse and complex carbon frameworks in recent years.[9] Among them, phosphine-catalyzed Michael addition of nucleophiles to electron-deficient alkenes has provided efficient C−C bond and C−X bond formations, in which zwitterions generated from Michael-type additions of phosphines to electron-deficient alkenes can act as organic bases to deprotonate protic nucleophiles (NuH) and catalyze the corresponding Michael additions to electron-deficient alkenes.[10] Herein, we describe a nucleophilic phosphine-catalyzed intramolecular Michael reaction of *N*-allylic substituted α-amino nitriles to prepare 2,4-disubstituted pyrrolidines (*N*-heterocyclic α-amino nitriles) via 5-*endo*-trig cyclizations.

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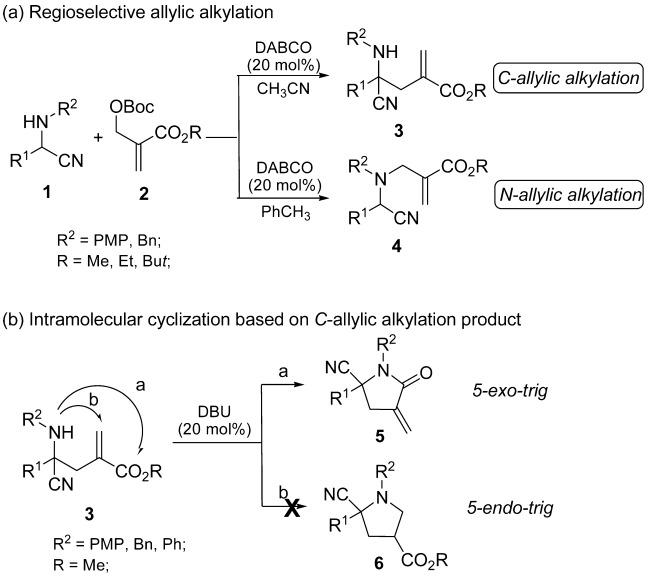
RESULTS AND DISCUSSION

In our previous work, we have demonstrated a metal-free controllable regioselective allylic alkylation and amination reaction between MBH adducts and α-amino nitriles, which utilized α-amino nitriles as dipronucleophiles and provided an efficient synthetic route for the preparation of multifuncationalized α-amino nitriles with high selectivity via a facile and unified approach (Scheme 1).[8a−c] In these works, we found that

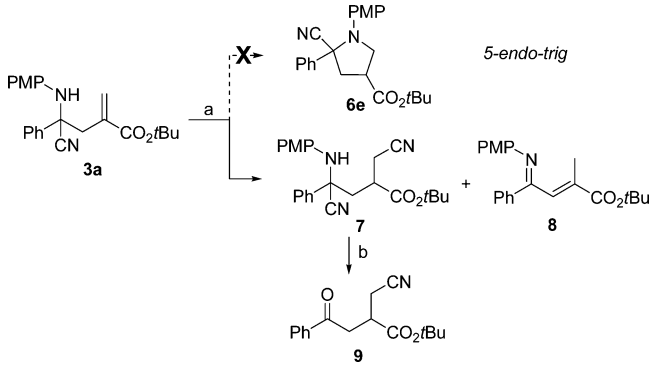
Scheme 1. Regioselective Allylic Alkylation and 5-*exo*-trig Cyclization of Compound 3



C-allylic alkylation products of α-amino nitriles can undergo 5-*exo*-trig cyclization to provide α-methylene-γ-butyrolactams in a metal-free catalytic fashion, whereas 5-*endo*-trig cyclization has not been observed. As part of our efforts to develop efficient metal-free processes to prepare a variety of functionalized nitriles incorporating quaternary carbon centers,[8] we became interested in the possibility of utilizing these functionalized allylic substituted α-amino nitriles to furnish diverse pyrrolidine rings bearing quaternary carbon centers through a nucleophile-driven 5-*endo*-trig cyclization. First, a *t*-butyl ester analogue of C-allylic alkylation product **3a**, which was prepared from a Strecker−allylic−alkylation sequence, was investigated to achieve 5-*endo*-trig cyclization because the bulky substituent of compound **3a** could inhibit the occurrence of favorable 5-*exo*-trig cyclization (Scheme 2). However, whether 5-*exo*-trig or 5-*endo*-trig, cyclization has not been observed with treatment of compound **3a** with a number of catalytic bases. Instead, this reaction gave the α-amino nitrile **7** and decyanation product **8**, which may derive from a base-induced dehydrocyanation and subsequent isomerization and recyanation. The structure of dicyano-substituted compound **7** was confirmed further by the conversion of **7** into ketone **9**. These results indicated that intramolecular 5-*endo*-trig cyclization of **3a**, which was counted on *N*-based nucleophilicity, was not advantaged.

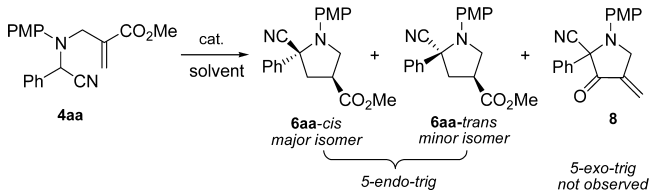
In view of the potential nucleophilicity of allylic substituted α-amino nitriles **4**, we conceived that the intramolecular 5-*endo*-trig cyclization of compound **4** could be achieved to afford the desired pyrrolidine rings. To assess the feasibility of this transformation, an initial investigation was examined with compound **4aa** in acetonitrile with a catalytic amount of DMAP

Scheme 2. Attempt of 5-*endo*-trig Cyclization of Compound 3



(20 mol %). Gratifyingly, this reaction gave rise to functionalized pyrrolidine **6aa** with a quaternary carbon atom incorporated, whose structure is unambiguously supported by ^{1}H NMR and ^{13}C NMR spectra and X-ray analysis (see the Supporting Information), albeit with poor yield and diastereoselectivity (Table 1, entry 1). DABCO gave a similar result as

Table 1. Optimization of 5-*endo*-trig Cyclization of Compound 4aa[a]



entry	cat.	solvent	*T* (°C)	*t* (h)	dr[b]	yield (%)[c]
1	DMAP	MeCN	60	24	1.1:1	15
2	DABCO	MeCN	60	24	1.1:1	14
3	PPh_3	MeCN	60	24		[d]
4	PBu_3	MeCN	30	1	1.4:1	81
5	DBU	MeCN	30	5.5	1.2:1	84
6	PBu_3	DCM	30	3	1.3:1	73
7	PBu_3	$CHCl_3$	30	24	1.2:1	18
8	PBu_3	THF	30	24	1.5:1	29
9	PBu_3	PhMe	30	24		trace
10	PBu_3	DMF	30	0.5	1.6:1	73
11	PBu_3	*t*-BuOH	30	7	1:1	72
12	PBu_3	MeCN	60	0.5	1.3:1	77
13	PBu_3	MeCN	0	1.5	1.5:1	89
14	PBu_3	MeCN	−30	2.5	1.6:1	90
15[e]	PBu_3	MeCN	0	1.5	1.6:1	92
16[f]	PBu_3	MeCN	0	2	2:1	96

[a]Reaction conditions: **4aa** (0.2 mmol) and catalyst (20 mol %) in solvent (2.0 mL). [b]Determined by ^{1}H NMR analysis of crude product. [c]Isolated yield. [d]No desired product was detected. [e]Catalyst (10 mol %) was used. [f]Catalyst (5 mol %) was used.

that of DMAP (Table 1, entry 2). In contrast, treatment of PPh_3 did not provided any desired product. To our delight, more electron-rich PBu_3 afforded the desired product efficiently at lower temperature in markedly increased yields (Table 1, entries 3 and 4). More basic Lewis base, such as DBU, was also employed and gave product **6aa** in good yield after a prolonged reaction time, which indicated that the reaction may undergo a general base-catalyzed process (Table 1, entry 5). Solvent

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optimization showed that this cyclization reaction proceeded well in polar solvent generally in the presence of 20 mol % PBu_3, while the diastereoselectivities of this transformation were unaffected (Table 1, entries 6−11). Noteworthily, 5-*exo*-trig cyclization of compound **4aa** was not detected in all screened reactions. Although the attempts to improve the diastereoselectivity of this transformation by employing the reaction at different temperatures have proven to be unsuccessful,[11] the yield of this reaction has been improved at low temperature (Table 1, entries 12−14). The further reducing the loading of catalyst enhanced the chemical yield markedly, and the reaction furnished the desired product **6aa** in excellent yield in the presence of PBu_3 (5 mol %) (Table 1, entries 15 and 16).

With optimal reaction conditions in hand, the scope and limitation of this phosphine-catalyzed intramolecular 5-*endo*-trig cyclization of functionalized α-amino nitriles **4** have been evaluated. The results are summarized in Table 2. Besides PMP

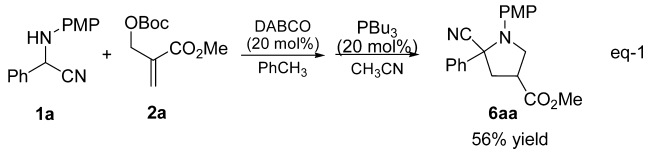
Table 2. Scope of 5-*endo*-trig Cyclization of Allylic Substituted α-Amino Nitriles 4[a]

entry	R^1	R^2	4	t (h)	dr[b]	yield (%)[c]
1	Ph	PMP	**4aa**	2	2:1	96 (**6aa**)
2	Ph	Ph	**4ba**	2	1.4:1	96 (**6ba**)
3	Ph	Bn	**4ca**	24	1.9:1	33 (**6ca**)
4	Ph	*n*Bu	**4da**	24		[d]
5	4-$MeOC_6H_4$	PMP	**4ab**	1	1.1:1	88 (**6ab**)
6	4-MeC_6H_4	PMP	**4ac**	1	1.5:1	92 (**6ac**)
7	4-ClC_6H_4	PMP	**4ad**	1	1.3:1	85 (**6ad**)
8	4-BrC_6H_4	PMP	**4ae**	1	1.1:1	88 (**6ae**)
9	3-$MeOC_6H_4$	PMP	**4af**	1	1.4:1	90 (**6af**)
10	2-BrC_6H_4	PMP	**4ag**	1	1.2:1	86 (**6ag**)
11[e,f]	2-naphthyl	PMP	**4ah**	2.5	2.1:1	81 (**6ah**)
12[e,f]	2-thienyl	PMP	**4ai**	3	1.2:1	72 (**6ai**)
13	*i*Pr	PMP	**4aj**	24		[d]

[a]Reaction conditions: **4** (0.2 mmol) and PBu_3 (5 mol %) in solvent (2.0 mL) at 0 °C. [b]Determined by ^1H NMR analysis of crude product. [c]Isolated yield. [d]No desired product was detected. [e]Catalyst (10 mol %) was used. [f]Run at 30 °C.

substituted α-amino nitriles **4**, *N*-phenyl substituted α-amino nitrile was also a suitable substrate to give the desired product **6** in good yield, whereas the reaction of the *N*-benzyl analogue proceeded sluggishly and provided the product in low yield (Table 2, entries 2 and 3). The cyclization of allylic substituted α-amino nitrile derived from aliphatic amine did not occur under the optimized reaction condition (Table 2, entry 4). These results indicated that sp^3-substituent (R^2) would decrease the acidity of the α-hydrogen of α-amino nitrile, which hampered the desired 5-*endo*-trig ring closure. On the basis of these, a variety of α-amino nitrile **4** with different substituents located at the α-position of the cyano group were investigated. The reaction proceeded well regardless of whether the aromatic group has an electron-withdrawing or an electron-donating group and whether the aromatic group is substituted at the *para*-, *meta*-, or *ortho*-position (Table 2, entries 5−10). β-Naphthyl and heteroaromatic subsititued α-amino nitrile can also serve as good substrates and provided the desired products in comparably good yields (Table 2, entries 11 and 12). However, aliphatic substituted α-amino nitrile did not provide any desired product, presumably due to the deficiency of the acidity of the substrate (Table 2, entry 13).

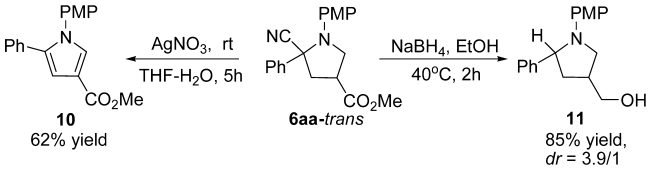
It is worth noting that the metal-free-catalyzed intramolecular 5-*endo*-trig cyclization can be accomplished via a tandem sequence (eq 1). In this manner, functionalized pyrrolidine **6aa**



can be readily obtained from available α-amino nitrile and MBH adduct **2a** via a one-pot reaction, which greatly enhances the efficiency of this method.

Finally, the synthetic transformations of functionalized pyrrolidine **6** were illustrated. The results are summarized in Scheme 3. The treatment of **6aa** with $AgNO_3$ in THF/H_2O solution afforded the unsaturated functionalized pyrrole **10** in 62% yield. Furthermore, *N*-heterocyclic α-amino nitrile **6aa** can be reduced to give the decyanation pyrrolidine **11** in 85% yield in the presence of $NaBH_4$ and EtOH.

Scheme 3. Chemical Transformations



CONCLUSION

In conclusion, we have demonstrated a novel nucleophilic phosphine-catalyzed 5-*endo*-trig cyclization of *N*-allylic substituted α-amino nitriles with the low catalyst loading, which provided an efficient synthetic route for the preparation of 2,4-disubstituted pyrrolidines (*N*-heterocyclic α-amino nitriles) incorporating multifunctional groups under mild reaction conditions. Furthermore, the synthesis of 2,4-disubstituted pyrrolidine via a one-pot sequence and the subsequent transformations of the functionalized products have also been demonstrated, which will find potential utility in organic synthesis.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Allylic Alkylation Compound 4. To a dried reaction tube were added **1a** (0.4 mmol), DABCO (20%), toluene (4 mL), and **2** (0.52 mmol). The mixture was stirred at 30 °C and was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give the crude products. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum (60−90 °C)) to provide the following compounds.[8b]

Methyl 2-(((Cyano(4-methoxyphenyl)methyl)(4-methoxyphenyl)amino)methyl)acrylate (Table 2, 4ab). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/15 as eluent, which afforded 119 mg of a colorless oil (81% yield). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38 (d, J = 8.9 Hz, 2H), 7.01−6.94 (m, 2H), 6.89 (dd, J = 9.3, 2.6 Hz, 2H), 6.84−6.73 (m, 2H), 6.19−6.18(m, 1H), 5.71−5.70 (m, 1H), 5.47 (s, 1H), 4.08 (d, J = 16.6 Hz, 1H), 3.89

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(d, J = 16.6 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 160.1, 156.1, 140.4, 136.3, 129.1, 127.4, 125.4, 123.0, 117.1, 114.6, 114.2, 59.7, 55.5, 55.4, 52.0, 50.7. IR (KBr, cm^{-1}): 2953, 2837, 2228, 1719, 1611, 1512, 1251, 1035, 834, 818. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ ($[M + H]^+$): 367.1652, found: 367.1658.

Methyl 2-(((Cyano(4-bromophenyl)methyl)(4-methoxyphenyl)amino)methyl)acrylate (Table 2, 4ae). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/15 as eluent, which afforded 80 mg of a light yellow oil (48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.03−6.92 (m, 2H), 6.85−6.72 (m, 2H), 6.21 (s, 1H), 5.71−5.70 (m, 1H), 5.44 (s, 1H), 4.10 (d, J = 16.1 Hz, 1H), 3.88 (d, J = 16.2 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.6, 156.5, 139.9, 136.2, 132.6, 132.1, 129.5, 127.8, 123.6, 123.3, 116.6, 114.7, 59.9, 55.6, 52.1, 51.6. IR (KBr, cm^{-1}): 2952, 2925, 2231, 1720, 1511, 1247, 1040, 832, 818. HRMS (ESI): calcd. for $C_{20}H_{20}BrN_2O_3$ ($[M + H]^+$): 415.0652, found: 415.0650.

Methyl 2-(((Cyano(thiophen-2-yl)methyl)(4-methoxyphenyl)amino)methyl)acrylate (Table 2, 4ai). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/15 as eluent, which afforded 63 mg of a light yellow oil (44% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (d, J = 5.0 Hz, 1H), 7.23−7.22 (m, 1H), 7.08−7.04 (m, 2H), 6.97 (dd, J = 5.0, 3.7 Hz, 1H), 6.87−6.80 (m, 2H), 6.24 (s, 1H), 5.78−5.77 (m, 1H), 5.61 (s, 1H), 4.16 (d, J = 16.6 Hz, 1H), 3.91 (d, J = 16.6 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 156.6, 140.0, 137.5, 136.0, 127.7, 127.7, 127.3, 126.9, 123.5, 116.3, 114.7, 56.9, 55.6, 52.1, 50.3. IR (KBr, cm^{-1}): 2951, 2837, 2232, 1719, 1511, 1247, 1040, 837, 818. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_3S$ ($[M + H]^+$): 343.1111, found: 343.1112.

General Procedure for the Synthesis of Pyrrolidine Derivatives 6. All reactions were carried out under a nitrogen atmosphere. To a dried reaction tube were added **4** (0.2 mmol), CH_3CN (2 mL), and PBu_3 (5%) at 0 °C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give the crude products. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum (60−90 °C)) to provide **6**.

Methyl 5-Cyano-1-(4-methoxyphenyl)-5-phenylpyrrolidine-3-carboxylate (Table 2, 6aa). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/20 as eluent, which afforded 65 mg of a colorless oil (97% yield, dr (*cis*/*trans*) = 2/1). **Major diastereomer** (**6aa**-*cis*): a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52−7.44 (m, 2H), 7.44−7.31 (m, 3H), 6.79−6.70 (m, 2H), 6.62−6.52 (m, 2H), 4.05 (dd, J = 9.2, 7.6 Hz, 1H), 3.89−3.83 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.39−3.28 (m, 1H), 3.23 (dd, J = 12.8, 8.5 Hz, 1H), 2.58 (dd, J = 12.8, 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 153.4, 139.6, 137.7, 129.4, 128.8, 125.3, 119.8, 116.7, 114.6, 65.8, 55.7, 52.8, 52.6, 47.5, 40.2. IR (KBr, cm^{-1}): 2953, 2835, 2231, 1738, 1512, 1247, 1036, 819, 778. HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_3$ ($[M + H]^+$): 337.1547, found: 337.1548. **Minor diastereomer** (**6aa**-*trans*): a white amorphous solid, mp: 105−107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54−7.47 (m, 2H), 7.40−7.31 (m, 3H), 6.78−6.64 (m, 2H), 6.63−6.50 (m, 2H), 4.20 (dd, J = 9.3, 7.3 Hz, 1H), 3.80 (t, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.62−3.47 (m, 1H), 2.99 (dd, J = 13.1, 7.3 Hz, 1H), 2.59 (dd, J = 13.1, 10.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.6, 153.3, 138.0, 138.0, 129.3, 128.9, 125.3, 119.6, 117.1, 114.5, 66.9, 55.6, 53.6, 52.5, 48.4, 40.6. IR (KBr, cm^{-1}): 2999, 2957, 2834, 2218, 1735, 1512, 1249, 1041, 819. HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_3$ ($[M + H]^+$): 337.1547, found: 337.1546.

Methyl 5-Cyano-1,5-diphenylpyrrolidine-3-carboxylate (Table 2, 6ba). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 59 mg of a colorless oil (96% yield, dr = 1.4:1). **Major diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45−7.43 (m, 2H), 7.40−7.32 (m, 3H), 7.19−7.15 (m, 2H), 6.81 (t, J = 7.3 Hz, 1H), 6.60 (d, J = 8.0 Hz, 2H), 4.09 (dd, J = 9.1, 7.6 Hz, 1H), 3.97−3.93 (m, 1H), 3.76 (s, 3H), 3.35−3.29 (m, 1H), 3.25 (dd, J = 12.6, 8.9 Hz, 1H), 2.60 (dd, J = 12.5, 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 143.4, 139.2, 129.5, 129.1, 128.9, 125.2, 119.7, 119.2, 115.0, 64.9, 52.7, 52.1, 47.6, 40.1. IR (KBr, cm^{-1}): 2958, 2868, 2232, 1740, 1600, 1507, 1346, 1219, 754, 704. HRMS (ESI): calcd. for $C_{19}H_{19}N_2O_2$ ($[M + H]^+$): 307.1441, found: 307.1444. **Minor diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50−7.48 (m, 2H), 7.38−7.32 (m, 3H), 7.15 (dd, J = 8.5, 7.5 Hz, 2H), 6.79 (t, J = 7.3 Hz, 1H), 6.58 (d, J = 8.2 Hz, 2H), 4.22 (t, J = 8.7 Hz, 1H), 3.90 (t, J = 9.1 Hz, 1H), 3.74 (s, 3H), 3.61−3.54 (m, 1H), 3.02 (dd, J = 13.1, 7.0 Hz, 1H), 2.59 (dd, J = 13.0, 11.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 143.8, 137.9, 129.4, 129.0, 128.9, 125.2, 119.5, 119.3, 115.5, 66.2, 53.1, 52.6, 48.7, 40.9. IR (KBr, cm^{-1}): 2953, 2851, 2226, 1738, 1601, 1503, 1323, 1201, 752, 699. HRMS (ESI): calcd. for $C_{19}H_{19}N_2O_2$ ($[M + H]^+$): 307.1441, found: 307.1440.

Methyl 1-Benzyl-5-cyano-5-phenylpyrrolidine-3-carboxylate (Table 2, 6ca). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/20 as eluent, which afforded 21 mg of a colorless oil (33% yield, dr = 1.8:1) as an unseparated mixture. **Major diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77−7.73 (m, 3H), 7.48−7.37 (m, 2H), 7.35−7.23 (m, 5H), 3.69 (s, 3H), 3.47−3.41 (m, 1H), 3.33−3.18 (m, 3H), 2.86−2.74 (m, 2H), 2.59 (dd, J = 13.6, 8.0 Hz, 1H). **Minor diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77−7.73 (m, 3H), 7.48−7.37 (m, 2H), 7.35−7.23 (m, 5H), 3.74−3.69 (m, 3H), 3.72 (s, 3H), 3.47−3.41 (m, 1H), 3.03 (dd, J = 13.9, 4.9 Hz, 1H), 2.86−2.74 (m, 1H), 2.39 (dd, J = 14.0, 11.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.1, 137.9, 137.8, 129.2, 129.2, 128.8, 128.6, 128.3, 128.2, 127.6, 127.5, 126.7, 126.5, 126.4, 117.7, 71.4, 70.3, 54.3, 54.2, 53.7, 53.5, 52.4, 49.2, 45.3, 44.9, 39.8, 39.5. HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_2$ ($[M + H]^+$): 321.1598, found: 321.1599.

Methyl 5-Cyano-1,5-bis(4-methoxyphenyl)pyrrolidine-3-carboxylate (Table 2, 6ab). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 65 mg of a colorless oil (88% yield, dr = 1.1:1). **Major diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40−7.36 (m, 2H), 6.92−6.88 (m, 2H), 6.77−6.72 (m, 2H), 6.60−6.55 (m, 2H), 4.02 (dd, J = 8.8, 8.1 Hz, 1H), 3.87−3.83 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.35−3.28 (m, 1H), 3.19 (dd, J = 13.0, 8.6 Hz, 1H), 2.55 (dd, J = 13.0, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 159.9, 153.4, 137.9, 131.4, 126.7, 116.9, 114.7, 114.6, 114.5, 65.4, 55.7, 55.5, 52.7, 52.6, 47.5, 40.2. IR (KBr, cm^{-1}): 2999, 2953, 2929, 2837, 2232, 1737, 1513, 1250, 1034, 833, 820. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ ($[M + H]^+$): 367.1652, found: 367.1652. **Minor diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44−7.39 (m, 2H), 6.91−6.85 (m, 2H), 6.74−6.69 (m, 2H), 6.60−6.54 (m, 2H), 4.18 (dd, J = 9.2, 7.3 Hz, 1H), 3.79 (s, 3H), 3.76−3.75 (m, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.55−3.48 (m, 1H), 2.95 (dd, J = 13.1, 7.4 Hz, 1H), 2.56 (dd, J = 13.1, 10.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 159.9, 153.3, 138.1, 129.8, 126.7, 119.7, 117.3, 114.7, 114.4, 66.6, 55.6, 55.5, 53.6, 52.6, 48.4, 40.5. IR (KBr, cm^{-1}): 2953, 2924, 2224, 1737, 1513, 1250, 1177, 833, 819. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ ($[M + H]^+$): 367.1652, found: 367.1653.

Methyl 5-Cyano-1-(4-methoxyphenyl)-5-*p*-tolylpyrrolidine-3-carboxylate (Table 2, 6ac). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 65 mg of a yellow oil (92% yield, dr = 1.5:1). **Major diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.76−6.72 (m, 2H), 6.60−6.54 (m, 2H), 4.04 (dd, J = 9.0, 7.6 Hz, 1H), 3.88−3.81 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.38−3.27 (m, 1H), 3.20 (dd, J = 12.8, 8.6 Hz, 1H), 2.55 (dd, J = 12.9, 7.7 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 153.4, 138.8, 137.9, 136.7, 130.1, 125.3, 119.9, 116.7, 114.6, 65.6, 55.7, 52.8, 52.6, 47.5, 40.2, 21.2. IR (KBr, cm^{-1}): 2953, 2922, 2851, 2233, 1738, 1513, 1247, 1038, 817. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_3$ ($[M + H]^+$): 351.1703, found: 351.1703. **Major diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.73−6.70 (m, 2H), 6.58−6.54 (m, 2H), 4.19 (dd, J = 9.2, 7.5 Hz, 1H), 3.78 (t, J = 9.4 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.56−3.49 (m, 1H), 2.96 (dd, J = 13.1, 7.3 Hz, 1H), 2.56 (dd, J = 13.1, 11.0 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 153.3, 138.8, 138.1, 135.0, 130.0, 125.3, 119.7, 117.2,

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114.5, 66.8, 55.6, 53.6, 52.5, 48.5, 40.6, 21.2. IR (KBr, cm^{-1}): 2950, 2925, 2930, 2226, 1731, 1512, 1243, 1039, 820. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_3$ ($[M + H]^+$): 351.1703, found: 351.1704.

Methyl 5-(4-Chlorophenyl)-5-cyano-1-(4-methoxyphenyl)-pyrrolidine-3-carboxylate (Table 2, 6ad). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 63 mg of a light yellow oil (85% yield, dr = 1.3:1). **Major diastereomer**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 9.0 Hz, 2H), 4.05 (t, J = 8.4 Hz, 1H), 3.85 (t, J = 8.6 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.36−3.27 (m, 1H), 3.23 (dd, J = 13.0, 8.3 Hz, 1H), 2.53 (dd, J = 13.0, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 153.7, 138.2, 137.5, 134.6, 129.6, 126.8, 119.4, 117.0, 114.6, 65.4, 55.7, 52.9, 52.7, 47.4, 40.2. IR (KBr, cm^{-1}): 2954, 2923, 2851, 2228, 1738, 1513, 1248, 1038, 812. HRMS (ESI): calcd. for $C_{20}H_{20}ClN_2O_3$ ($[M + H]^+$): 371.1157, found: 371.1153. **Minor diastereomer**: ^1H NMR (300 MHz, $CDCl_3$) δ: 7.50−7.42 (m, 2H), 7.37−7.31 (m, 2H), 6.74−6.70 (m, 2H), 6.57−6.51 (m, 2H), 4.19 (dd, J = 9.3, 7.1 Hz, 1H), 3.84−3.75 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.58−3.47 (m, 1H), 2.98 (dd, J = 13.2, 7.4 Hz, 1H), 2.55 (dd, J = 13.2, 10.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 153.6, 137.7, 136.7, 134.8, 129.6, 126.9, 119.2, 117.4, 114.6, 66.5, 55.6, 53.7, 52.6, 48.3, 40.6. IR (KBr, cm^{-1}): 2955, 2924, 2853, 2224, 1738, 1513, 1248, 1038, 819. HRMS (ESI): calcd. for $C_{20}H_{20}ClN_2O_3$ ($[M + H]^+$): 371.1157, found: 371.1153.

Methyl 5-(4-Bromophenyl)-5-cyano-1-(4-methoxyphenyl)-pyrrolidine-3-carboxylate (Table 2, 6ae). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 73 mg of a light yellow oil (88% yield, dr = 1.1:1). **Major diastereomer**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 6.78−6.72 (m, 2H), 6.60−6.51 (m, 2H), 4.08−4.02 (m, 1H), 3.87−3.82 (m, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.34−3.28 (m, 1H), 3.22 (dd, J = 13.1, 8.2 Hz, 1H), 2.53 (dd, J = 13.0, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 153.7, 138.8, 137.4, 132.6, 127.1, 123.0, 119.3, 117.0, 114.6, 65.4, 55.7, 52.9, 52.7, 47.3, 40.2. IR (KBr, cm^{-1}): 2997, 2954, 2927, 2852, 2234, 1737, 1513, 1247, 1036, 819. HRMS (ESI): calcd. for $C_{20}H_{20}BrN_2O_3$ ($[M + H]^+$): 415.0652, found: 415.0647. **Minor diastereomer**: ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51−7.48 (m, 2H), 7.40−7.37 (m, 2H), 6.76−6.70 (m, 2H), 6.57−6.51 (m, 2H), 4.19 (dd, J = 9.4, 7.1 Hz, 1H), 3.82−3.77 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.58−3.47 (m, 1H), 2.97 (dd, J = 13.0, 7.5 Hz, 1H), 2.55 (dd, J = 13.2, 10.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 153.6, 137.6, 137.3, 132.6, 127.2, 122.9, 119.2, 117.4, 114.6, 66.5, 55.6, 53.7, 52.6, 48.2, 40.6. IR (KBr, cm^{-1}): 2952, 2923, 2852, 2225, 1737, 1513, 1248, 1036, 819. HRMS (ESI): calcd. for $C_{20}H_{20}BrN_2O_3$ ($[M + H]^+$): 415.0652, found: 415.0645.

Methyl 5-Cyano-5-(3-methoxyphenyl)-1-(4-methoxyphenyl)pyrrolidine-3-carboxylate (Table 2, 6af). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/20 as eluent, which afforded 66 mg of a colorless oil (90% yield, dr = 1.4:1). **Major diastereomer**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.33−7.28 (m, 1H), 7.09−7.02 (m, 2H), 6.89−6.85 (m, 1H), 6.78−6.72 (m, 2H), 6.61−6.54 (m, 2H), 4.07−4.02 (m, 1H), 3.87−3.81 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.38−3.30 (m, 1H), 3.21 (dd, J = 13.1, 8.7 Hz, 1H), 2.58 (dd, J = 13.1, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 160.5, 153.4, 141.4, 137.8, 130.5, 119.8, 117.5, 116.7, 114.6, 114.0, 111.2, 65.8, 55.7, 55.5, 52.8, 52.6, 47.4, 40.3. IR (KBr, cm^{-1}): 2924, 2851, 2230, 1738, 1514, 1248, 1040, 820. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ ($[M + H]^+$): 367.1652, found: 367.1653. **Minor diastereomer**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.04−7.03 (m, 1H), 6.85 (dd, J = 8.2, 2.3 Hz, 1H), 6.74−6.71 (m, 2H), 6.58−6.55 (m, 2H), 4.19 (dd, J = 9.2, 7.3 Hz, 1H), 3.80−3.78 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.56−3.49 (m, 1H), 2.98 (dd, J = 13.1, 7.4 Hz, 1H), 2.59 (dt, J = 13.0, 9.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.6, 160.4, 153.3, 139.8, 138.1, 130.5, 119.6, 117.6, 117.1, 114.5, 114.2, 111.1, 66.9, 55.6, 55.5, 53.6, 52.6, 48.3, 40.6. IR (KBr, cm^{-1}): 2954, 2924, 2851, 2274, 1738, 1513, 1248, 1038, 818. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ ($[M + H]^+$): 367.1652, found: 367.1658.

Methyl 5-(2-Bromophenyl)-5-cyano-1-(4-methoxyphenyl)-pyrrolidine-3-carboxylate (Table 2, 6ag). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/20 as eluent, which afforded 71 mg of a light yellow oil (86% yield, dr = 1.2:1). **Major diastereomer**: ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69 (dd, J = 7.6, 1.5 Hz, 1H), 7.48−7.45 (m, 1H), 7.33−7.26 (m, 1H), 7.25−7.20 (m, 1H), 6.85−6.75 (m, 2H), 6.62−6.53 (m, 2H), 4.05−3.97 (m, 1H), 3.90−3.84 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.30−3.12 (m, 2H), 3.05−2.96 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.8, 153.4, 137.3, 135.9, 135.7, 130.6, 129.6, 127.8, 120.1, 118.5, 116.4, 114.5, 55.7, 52.6, 52.2, 44.5, 40.5. IR (KBr, cm^{-1}): 2953, 2926, 2853, 2232, 1738, 1513, 1248, 1030, 818, 761. HRMS (ESI): calcd. for $C_{20}H_{20}BrN_2O_3$ ($[M + H]^+$): 415.0652, found: 415.0654. **Minor diastereomer**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.60 (d, J = 7.6 Hz, 2H), 7.32−7.29 (m, 1H), 7.19 (td, J = 7.7, 1.6 Hz, 1H), 6.75 (d, J = 8.9 Hz, 2H), 6.54 (d, J = 8.7 Hz, 2H), 4.20 (t, J = 7.9 Hz, 1H), 3.79 (t, J = 8.8 Hz, 1H), 3.70 (s, 3H), 3.67 (brs, 3H), 3.61−3.48 (m, 1H), 3.31−3.07 (m, 1H), 3.01−2.85 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 153.1, 130.5, 127.9, 114.5, 55.6, 52.5, 43.9, 40.8. IR (KBr, cm^{-1}): 2952, 2925, 2853, 2224, 1738, 1513, 1248, 1033, 817, 760. HRMS (ESI): calcd. for $C_{20}H_{20}BrN_2O_3$ ($[M + H]^+$): 415.0652, found: 415.0655.

Methyl 5-Cyano-1-(4-methoxyphenyl)-5-(naphthalen-2-yl)-pyrrolidine-3-carboxylate (Table 2, 6ah). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 63 mg of a white amorphous solid (81% yield, dr = 2.1:1). **Major diastereomer**: mp 119−121 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.91−7.82 (m, 3H), 7.57−7.50 (m, 3H), 6.73−6.69 (m, 2H), 6.65−6.60 (m, 2H), 4.15−4.10 (m, 1H), 3.91 (t, J = 8.7 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.40 (p, J = 8.0 Hz, 1H), 3.43−3.37 (m, 1H), 2.65 (dd, J = 13.2, 8.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 153.6, 137.9, 137.0, 133.4, 133.3, 129.7, 128.4, 127.9, 127.0, 127.0, 124.9, 122.5, 119.8, 117.0, 114.6, 66.2, 55.6, 53.0, 52.7, 47.4, 40.4. IR (KBr, cm^{-1}): 2956, 2927, 2853, 2226, 1739, 1514, 1255, 1033, 818, 764. HRMS (ESI): calcd. for $C_{24}H_{23}N_2O_3$ ($[M + H]^+$): 387.1703, found: 387.1702. **Minor diastereomer**: mp 121−123 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J = 1.8 Hz, 1H), 7.87−7.81 (m, 3H), 7.55−7.47 (m, 3H), 6.71−6.66 (m, 2H), 6.63−6.57 (m, 2H), 4.26 (dd, J = 9.3, 7.2 Hz, 1H), 3.85 (t, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.62−3.54 (m, 1H), 3.03 (dd, J = 13.2, 7.4 Hz, 1H), 2.69 (dd, J = 13.2, 10.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 153.4, 138.0, 135.6, 133.4, 133.3, 129.7, 128.3, 127.8, 126.9, 125.1, 122.3, 120.1, 119.6, 117.2, 114.5, 67.2, 55.6, 53.7, 52.6, 48.2, 40.7. IR (KBr, cm^{-1}): 2952, 2924, 2853, 2224, 1730, 1513, 1238, 1033, 815, 763. HRMS (ESI): calcd. for $C_{24}H_{23}N_2O_3$ ($[M + H]^+$): 387.1703, found: 387.1701.

Methyl 5-Cyano-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-pyrrolidine-3-carboxylate (Table 2, 6ai). Purified by silica gel chromatography using a mixture of EtOAc/petroleum ether = 1/25 as eluent, which afforded 49 mg of a light yellow oil (72% yield, dr = 1.4:1.) as an unseparated mixture. **Major diastereomer**: ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30−7.25 (m, 1H), 7.23 (dd, J = 3.7, 1.3 Hz, 1H), 6.99 (dd, J = 5.1, 3.7 Hz, 1H), 6.79−6.70 (m, 4H), 3.99−3.93 (m, 1H), 3.78 (s, 3H), 3.77−3.73 (m, 1H), 3.72 (s, 3H), 3.53−3.42 (m, 1H), 3.23 (dd, J = 13.2, 8.9 Hz, 1H), 2.72 (dd, J = 13.3, 8.1 Hz, 1H). **Minor diastereomer**: ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30−7.25 (m, 2H), 6.95 (dd, J = 5.1, 3.6 Hz, 1H), 6.79−6.70 (m, 4H), 4.14 (dd, J = 9.4, 6.9 Hz, 1H), 3.77−3.73 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.53−3.42 (m, 1H), 3.05 (dd, J = 13.2, 7.4 Hz, 1H), 2.80 (dd, J = 13.2, 10.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 172.0, 154.2, 154.1, 145.6, 143.2, 138.0, 137.7, 127.4, 126.9, 126.8, 126.6, 126.2, 125.2, 119.0, 118.1, 117.6, 114.6, 114.5, 114.4, 63.8, 63.0, 62.9, 55.6, 55.6, 53.6, 52.8, 52.6, 48.6, 47.7, 40.4, 40.3. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_3S$ ($[M + H]^+$): 343.1111, found: 343.1112.

***tert*-Butyl 4-Cyano-2-(cyanomethyl)-4-(4-methoxyphenylamino)-4-phenylbutanoate (Scheme 2, 7).** To a dried flask were added **3aa** (0.2 mmol), DBU (20%), and CH_3CN (2 mL) under a nitrogen atmosphere. The mixture was stirred at 60 °C, and the reaction was monitored by TLC. Upon completion, the resulting mixture was concentrated under reduced pressure, and the residue was

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purified through column chromatography on silica gel (EtOAc/petroleum ether = 1/10) to provide compounds **7** and **8**.

Compound **7**: an unseparated mixture (a colorless oil, 40 mg, 49% yield. dr = 1.7/1). **Major diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93−7.78 (m, 1H), 7.48−7.46 (m, 2H), 7.13−7.09 (m, 2H), 6.68−6.65 (m, 2H), 6.54−6.51 (m, 2H), 3.71 (s, 3H), 3.37−3.18 (m, 2H), 3.11−3.03 (m, 1H), 2.93 (s, 1H), 2.88−2.81 (m, 1H), 2.32 (dd, J = 6.7, 3.8 Hz, 1H), 1.48 (s, 9H). **Minor diastereomer**:^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28−7.23 (m, 5H), 6.94−6.91 (m, 2H), 6.76−6.73 (m, 2H), 3.82 (s, 3H), 3.74−3.68 (m, 1H), 3.37−3.18 (m, 2H), 3.04−2.97 (m, 1H), 2.93−2.91 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.4, 170.4, 167.1, 166.3, 156.4, 156.1, 143.6, 143.2, 138.2, 137.5, 130.8, 128.9, 128.9, 128.5, 127.8, 127.7, 125.8, 122.3, 120.4, 118.4, 114.7, 114.0, 83.0, 82.0, 55.6, 55.4, 40.6, 40.6, 39.2, 31.2, 28.1, 28.0, 19.5, 19.2. HRMS (ESI): calcd. for $C_{24}H_{28}N_3O_3$ ($[M + H]^+$): 406.2125, found 406.2114.

***tert*-Butyl 4-(4-Methoxyphenylimino)-2-methyl-4-phenylbut-2-enoate (Scheme 2, 8).** A colorless oil (29 mg, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85−7.82 (m, 2H), 7.47−7.30 (m, 3H), 7.21−7.20 (m, 3H),, 6.91−6.83 (m, 4H), 3.81 (s, 3H), 1.53 (d, J = 1.3 Hz, 3H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3, 164.2, 157.0, 143.9, 138.3, 134.9, 134.2, 130.8, 128.7, 128.1, 122.5, 114.0, 81.2, 55.6, 28.2, 15.5. IR (KBr, cm^{-1}): 2977, 2932, 2835, 1709, 1606, 1503, 1245, 1168, 1123, 1036, 848, 746. HRMS (ESI): calcd. for $C_{22}H_{26}NO_3$ ($[M + H]^+$): 352.1907, found: 352.1906.

***tert*-Butyl 2-(Cyanomethyl)-4-oxo-4-phenylbutanoate (Scheme 2, 9).** Compound **7** (37.8 mg, 0.1 mmol) was dissolved in THF (0.68 mL) and treated with an aqueous solution (0.1 mL) of $AgNO_3$ (33.9 mg, 0.2 mmol).[12] After stirring at room temperature for 2 h, the mixture was filtrated through a pad of Celite and the precipitate was washed with ether (2 × 5 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were washed with brine (2 × 5 mL) and water (5 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed in *vacuo*. Purification by flash chromatography (silica gel, EtOAc/petroleum 1/8) afforded compound **9** (21 mg, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01−7.94 (m, 2H), 7.64−7.56 (m, 1H), 7.53−7.45 (m, 2H), 3.57 (dd, J = 17.7, 5.3 Hz, 1H), 3.37−3.22 (m, 3H), 2.82 (d, J = 6.2 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.9, 170.8, 136.3, 133.8, 128.9, 128.2, 118.0, 82.6, 38.7, 37.9, 28.0, 19.4. IR (KBr, cm^{-1}): 2979, 2922, 2851, 2248, 1730, 1685, 1369, 1156, 846, 755. HRMS (ESI): calcd. for $C_{16}H_{20}NO_3$ ($[M + H]^+$): 274.1438, found: 274.1438.

General Procedure for the Tandem Sequence (eq 1). To a dried reaction tube were added **1a** (48 mg, 0.2 mmol), DABCO (20%), toluene (1 mL), and **2a** (56 mg, 0.26 mmol) under a nitrogen atmosphere. The mixture was stirred at 30 °C and was monitored by TLC. Upon completion, CH_3CN (1 mL) and PBu_3 (20%) were added in turn at 0 °C. After 2.5 h, the mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, EtOAc/petroleum (60−90 °C)) to provide compound **6aa** (38 mg, 56% yield).

Methyl 1-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (Scheme 3, 10). **6aa** (33.6 mg, 0.1 mmol) was dissolved in THF (0.68 mL) and treated with an aqueous solution (0.1 mL) of $AgNO_3$ (33.9 mg, 0.2 mmol). After stirring at room temperature for 5 h, the solution was filtrated through a pad of Celite and the precipitate was washed with ether (2 × 5 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were washed with brine (2 × 5 mL) and water (5 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed in vacuo. Purification by flash chromatography (silica gel, EtOAc/petroleum = 1/10) afforded compound **10** (19 mg, 62% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (s, 1H), 7.25−7.20 (m, 3H), 7.12−7.11 (m, 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.81 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 159.0, 135.2, 132.7, 132.1, 129.1, 128.5, 128.3, 127.1, 127.1, 116.3, 114.4, 110.7, 55.6, 51.3. IR (KBr, cm^{-1}): 2952, 2932, 2853, 1718, 1513, 1249, 1154, 1033, 837, 762, 697. HRMS (ESI): calcd. for $C_{19}H_{18}NO_3$ ($[M + H]^+$): 308.1281, found: 308.1284.

(1-(4-Methoxyphenyl)-5-phenylpyrrolidin-3-yl)methanol (Scheme 2, 11). **6aa** (33.6 mg, 0.1 mmol) was dissolved in THF (0.1 mL) and treated with an EtOH solution (0.1 mL) of $NaBH_4$ (11 mg, 0.3 mmol). After stirring at 40 °C for 2 h, the solution was treated with 1 N HCl (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (2 × 5 mL) and water (5 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed in *vacuo*. Purification by flash chromatography (silica gel, EtOAc/petroleum = 1/3) afforded the product **11** (23 mg, 85% yield, dr = 3.9/1) as an unseparated mixture. **Major diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.19 (m, 5H), 6.72 (d, J = 9.0 Hz, 2H), 6.45 (d, J = 8.9 Hz, 2H), 4.61 (t, J = 7.3 Hz, 1H), 3.69 (s, 3H), 3.66−3.64 (m, 3H), 3.57−3.60 (m, 1H), 2.63−2.52 (m, 2H), 1.78−1.73 (m, 1H). **Minor diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.19 (m, 5H), 6.75 (d, J = 9.0 Hz, 2H), 6.42 (d, J = 9.0 Hz, 2H), 4.71 (d, J = 7.3 Hz, 1H), 3.84−3.81 (m, 1H), 3.70 (s, 3H), 3.66−3.64 (m, 2H), 3.18 (t, J = 8.8 Hz, 1H), 2.69−2.65 (m, 1H), 2.24−2.17 (m, 1H), 2.01−1.98 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 151.3, 144.8, 142.5, 128.8, 128.7, 126.8, 126.0, 126.0, 116.7, 115.0, 114.7, 114.5, 113.0, 106.5, 65.5, 65.1, 63.8, 63.4, 56.0, 55.9, 54.4, 52.7, 40.5, 40.2, 39.1, 38.9. HRMS (ESI): calcd. for $C_{18}H_{22}NO_2$ ($[M + H]^+$): 284.1645, found: 284.1649.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of products **4ab**, **4ae**, **4ai**, **6aa**−**6ca**, **6ab**−**6ai**, **7**, **8**, **9**, **10**, and **11**, as well as X-ray structure of compound **6aa**-*trans*. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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