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A Convenient Method for Preparation of α-Imino Carboxylic Acid Derivatives and Application to the Asymmetric Synthesis of Unnatural α-Amino Acid Derivative

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We describe herein a manganese(IV) oxide-mediated oxidation of *N*-*p*-methoxyphenyl (PMP)-protected glycine derivatives for the synthesis of α-imino carboxylic acid derivatives. Using this methodology, utilization of unstable glyoxic acid derivatives was avoided. Furthermore, using this methodology we synthesized novel α-imino carboxylic acid derivatives such as α-imino phenyl ester, perfluoroalkyl etsers, imides, and thioester. The asymmetric Mannich reaction of those novel imine derivatives with 1,3-dicarbonyl compound is also described, and the novel α-imino imide gave improved chemical yield and stereoselectivity compared with those obtained by the use of the conventional α-imino ester-type substrate.

Key words α-imino carboxylic acid derivative; heterogeneous oxidant; asymmetric organocatalysis; thiourea; unnatural α-amino acid

Unnatural α-amino acids are often seen in varieties of biologically active compounds,[1–4] including pharmaceutics, and have been used as indispensable chiral building blocks for the synthesis of such active compounds.[5,6] Additionally, increasing utilities of unnatural amino acids as a key structural element have also been shown in fields of chemical biology and asymmetric transformation.[7–11] These contexts evoke much interest of synthetic chemists in asymmetric synthesis of the structural unit.[12,13] Enabling easy access to diverse α-amino acids only by changing nucleophiles employed, Mannich-type reaction of α-imino ester has been widely utilized for the asymmetric synthesis.[14–20] Generally, condensation of glyoxalates and primary amines affords α-imino esters as the requisite substrate for Mannich-type reaction (Chart 1a); however, the glyoxalates are unstable, and suffer easy hydrolysis or polymerization at room temperature. Additionally, high susceptibility of the resulting α-imino ester to silica gel has forced us to directly use the imino esters for the Mannich reaction without purification, thereby leading to difficulty in maintaining the reaction outcome. In this context, cross-dehydrogenative coupling (CDC) has been investigated for the synthesis of α-functionalized amino acids[21–23] (Chart 1b). The CDC protocol features oxidative preparation of α-imino ester from glycinates with the use of the oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), CuOAc, $Ru(bpy)_3Cl_2$/light (or *N*-oxyl radical), or Cu(I)/molecular oxygen, followed by *in situ* Mannich reaction. Although the CDC protocol is free from the use of unstable glyoxalates, the *in situ* Mannich reaction has to be performed in the presence of the employed oxidant due to difficulty in achieving complete separation of the imino ester and oxidant, by which the use of the CDC remains within application to the coupling of oxidant-tolerant functional units. Here, we envisioned that the heterogeneous oxidation system enabling facile removal of insoluble oxidants by filtration allowed the imino ester to be readily obtained and subsequently subjected to Mannich reaction under oxidant-free conditions (Chart 1c).

Among a wide variety of oxidants, manganese(IV) oxide is potential choice of heterogeneous oxidant.[24,25] The mild oxidative potential and easily separable nature allow manganese(IV) oxide to be favorably utilized in the oxidative transformation at the near final step of complex molecules such as natural products. Although manganese(IV) oxide-mediated conversion of aliphatic amines to the corresponding imines mainly consisting of *N*-heteroaromatization of cyclic amines has been reported,[26,27] application to the synthesis of α-imino ester remains to be reported.[28] Being potentially applied to *N*-protected glycine derivatives possessing replacement of the ester function with other carboxylic acid equivalents such as amide or imide, the envisioned oxidative protocol could expand its substrate scope to barely accessible molecules by addition-dehydration sequence for the imine formation. Such amides or imides could provide an additional site for formation of an intermediary complex (substrate–catalyst–nucleophile) involved in the following asymmetric Mannich reaction.

Results and Discussion

One critical issue involved in the oxidation using manganese(IV) oxide is quality of the reagent. Generally, activated manganese(IV) oxide has been reported to be suitable for the MnO_2-mediated oxidative conversion of various substrates. Thus, we initially subjected *N*-*p*-methoxyphenyl (PMP) glycine ethylester **1a** to oxidation in CH_2Cl_2 using 20 eq of activated manganese(IV) oxide from commercial source. The attempted reaction resulted in complete disappearance of **1a** within 1 h to give desired imine **2a** only by filtration through Celite; however, several byproducts derived from overoxidation were detected (see Supplementary materials). On the other hand, the use of less expensive and non-activated powdered manganese oxide(IV) could afford better result, in which desired imine **2a** with satisfactory purity was obtained in 92% isolated yield by simple filtration work-up on Celite pad (Table 1, entry 1). Next, applicability of the oxida-

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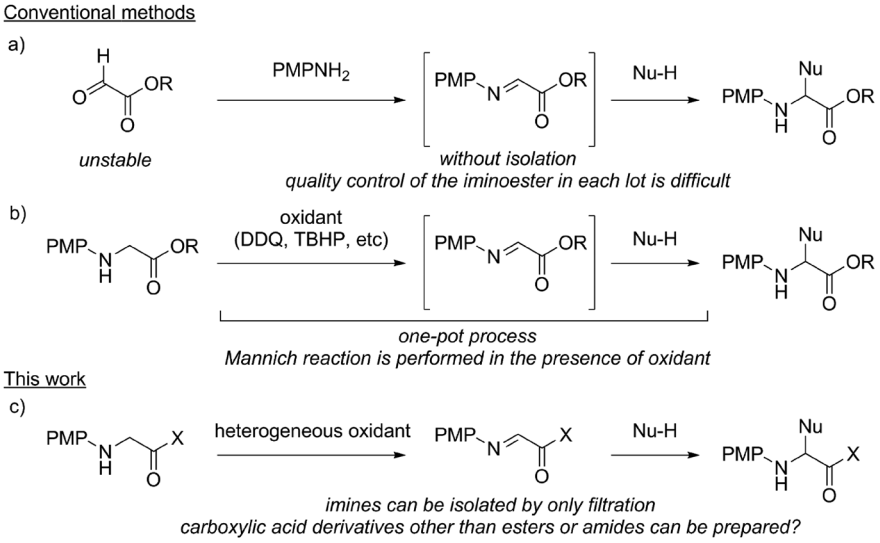
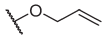
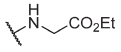
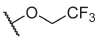
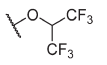
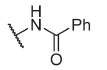
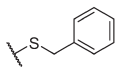


Chart 1. Synthesis of α-Amino Acids *via* α-Imino Carboxylic Acids

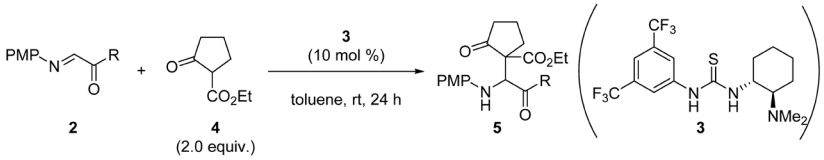
Table 1. Synthesis of α-Imino Carboxylic Acid Derivatives[a]

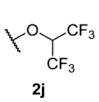
entry	R	1	time (min)	2	yield (%)[b]
1		**1a**	60	**2a**	93
2		**1b**	60	**2b**	92
3		**1c**	60	**2c**	98
4		**1d**	60	**2d**	90
5		**1e**	60	**2e**	87
6[c]		**1f**	60	**2f**	95
7		**1g**	60	**2g**	99
8		**1h**	30	**2h**	92
9		**1i**	60	**2i**	98
10		**1j**	60	**2j**	88
11		**1k**	45	**2k**	96
12		**1l**	60	**2l**	91
13		**1m**	30	**2m**	quant

[a]The reaction was conducted with **1** (1.00 mmol) and MnO_2 (20.0 mmol) in CH_2Cl_2 (100 mL) at room temperature. [b]Yield of the crude product after filtration through Celite®. [c]For this entry, 25.0 mmol of MnO_2 was used.

tion system to various carboxylic functionalities was examined. Oxidation of methyl, *t*-butyl, benzyl, or allyl glycinate with the non-activated manganese oxide(IV) in CH_2Cl_2 at room temperature for 1 h proceeded efficiently to give desired highly homogeneous imine in high chemical yield (Table 1, entries 2–5). Resulting imino esters **2b**–**e** are substrates of great use for the following asymmetric Mannnich reaction, because such ester functionalities can be generally cleaved without affecting enantiometric purity using acidic reagent,[29] hydrogenation,[30] and Pd-catalyzed reaction,[31] respectively. We next examined the synthesis of imino amides **2f** and **g**, of great value in Petasis reaction, using boric or boronate reagent. Although laborious and time-consuming steps were required for the preparation of such imino amides using the conventional addition-dehydration sequence, dipeptide-type compound PMP-Gly-Gly-OEt **1f** and glycyl *N*-ethyl anilide **1g** were successfully converted to the corresponding imino amides **2f** and **g** by the action of manganese(IV) oxide. Petasis reaction of the resulting imino amide **2f** with aryl boric acids was reported to afford aryl glycine derivatives.[32] Furthermore, Takemoto *et al.* described that asymmetric Petasis reaction of substrate such as **2g** with vinyl boronate in the presence of a hydroxyl thiourea-type organocatalyst furnished satisfactory results.[33] Next, we attempted the synthesis of novel imine derivatives, never accessible by the conventional procedure, using the heterogeneous manganese(IV) oxide-meditated oxidation. The novel imines **2h**–**j**, which possess highly-activated ester moieties such as phenyl, trifluoroethyl, or hexafluoroisopropyl esters could be prepared by our strategy (entries 8–10). Furthermore, attempted reactions led to almost quantitative formation of desired imino imides **2k** and **l** with high purity (entries 11, 12). Surprisingly, even thioester **2m**, susceptible to an oxidant, could be prepared without any problems (entry 13). Although other protections except for PMP were also examined, we failed to find suitable protective groups (see Supplementary materials). The derivative **1n**, with electron donating methoxy substituent both on the *para*- and *ortho*-positions of the phenyl ring, suffered auto-oxidation by atmospheric oxygen during purification of **1n**. Oxidation of *ortho* methoxy phenyl-protected derivative **1o** proceeded more slow-

Table 2. Asymmetric Mannich Reaction of α-Imino Carboxylic Acid Derivatives[a]



entry	R	5	yield (%)[b]	dr[c]	ee of each diastereomer (%)[d]
1	 2a	**5a**	25	57:43	84, 36
2	 2h	**5b**	31	51:49	51, 7
3	 2i	**5c**	0	--	--
4	 2j	**5d**	0	--	--
5	 2k	**5e**	77	61:39	92,52
6	 2l	**5f**	0	--	--
7	 2m	**5g**	40	51:49	82, 56
8[e]	 2k	**5e**	0	--	--

[a]The reaction was conducted with **2** (1.0 equiv.), **4** (2.0 equiv.) and **3** (10 mol %) in toluene at room temperature for 24 h. [b]Yield of the isolated product. [c]Estimated by chiral HPLC analysis. [d]Determined by chiral HPLC analysis. [e]The reaction was performed in the presence of MnO_2.

ly than that of PMP-protected substrate, probably due to steric hindrance, and resulted in incomplete reaction. Increasing amount of the oxidant led to formation of a complex mixture. Other protections including benzyl (Bn), *tert*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc), and triphenylmethyl (Trt) also failed to afford the corresponding imines. Thus, we decided to continue our investigation using *N*-PMP protection.

Having several types of α-imino carbonyl derivatives **2h**–**m** obtained in hand, we evaluated asymmetric Mannich reaction of the resulting imine in the presence of Takemoto's chiral bifunctional thiourea catalyst **3**[34] compared with that of conventional α-imino ethyl ester **2a** (Table 2). Initially, attempted asymmetric Mannich reaction of the ethyl α-imino carboxylate **2a** with β-ketoester **4** gave the corresponding Mannich adducts **5a** as diastereomixture in low chemical yield. The enantiomeric excess of one of the diastereomers was good (entry 1). The reaction of phenyl ester-type substrate **2h** also produced the adduct **5b**, albeit with diminished enantioselectivities (entry 2). To our surprise, the perfluoroalkyl ester-type substrates **2i** and **j** did not give the desired products at all (entries 3, 4). Further exploration revealed that the reaction of the imino imide **2k** proceeded smoothly to yield the corresponding Mannich adduct **5e** in higher chemical yield and enantioselectivities compared with those of the reaction using **2a** (entry 5). On the other hand, the reaction of another type of imide, benzimide-type substrate **2l** did not proceed under the same condition (entry 6). Unfortunately, the chemical yield of the reaction using α-imino thioester **2m** was moderate (entry 7). Although the reason the reaction rate of **2k** was superior to that of **2a** remains to be disclosed, we speculate that the interaction of the carbonyl group in the five-membered ring with the thiourea catalysts contributes to the acceleration of the Mannich reaction leading to improvement of enatioselectivity. The two carbonyl groups of the other type of imide **2l** might have different orientation from those of **2k** and this might cause the difference of the reactivities of those substrates. We are currently performing further studies such as computational analysis for elucidation of the reaction mechanism including origins of stereo selection. Being performed in the presence of manganese(IV) oxide, thiourea 4-catalyzed Mannich reaction of **2k** and **3** did not proceed under the oxidative condition that the employed catalyst was decomposed (entry 8). This result indicates that removal of the oxidant after the formation of imine is indispensable for the success of the present process.

Summary

We developed a novel and simple protocol for the synthesis of α-imino carboxylic acid derivatives by manganese(IV) oxide-mediated oxidation of glycine derivatives. This protocol enables the synthesis of α-iminocarboxylic acid derivatives such as phenyl ester, perfluoroalkyl esters, imides, and thioester, which could not be prepared by conventional synthetic procedure, and contributes an extension of the substrate scopes for the synthesis of unnatural α-amino acid derivatives. Further examination of the reaction scope of the oxidation and application of the resulting imines for asymmetric synthesis of unnatural α-amino acid derivatives are currently under way.

Experimental

General Methods All reactions were carried out under a positive pressure of argon. Analytical TLC was performed on Merck TLC silica gel $60F_{254}$ silica gel plates. Visualization was accomplished with molibudenium phosphate, *p*-anisaldehyde, Hannessian's cocktail or ninhydrin. For column chromatography, silica gel (KANTO KAGAKU N-60) was employed. NMR spectra were recorded using a Bruker AV400N at 400 MHz frequency or JEOL JNM-AL300 for ^{1}H, and JEOL JNM-AL300 at 75 MHz frequency for ^{13}C in the stated solvents using tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard (NMR descriptions: s, singlet; d, doublet; t, triplet; q, quartet; hept, heptet; m, multiplet; br, broad). Coupling constants, *J*, are reported in Hertz. For chiral HPLC analysis, a chiralpak IA (DAICEL, 4.6×250 mm), a chiralcel IB-3 (DAICEL, 4.6×250 mm) or a chiralcel IC-3 (DAICEL, 4.6×250 mm) were employed and eluting products were detected by UV at 254 nm. A solvent system consisting of HPLC grade of hexane and 2-propanol was used for HPLC analysis. Mass spectra were recorded on a Waters MICROMASS® LCT PREMIERTM (electrospray ionization-time-of-flight (ESI-TOF)). Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in g dL^{-1}). IR was measured using a JEOL FT-IR 6200. Melting point was determined on YANAGIMOTO micro melting point apparatus. Elemental combustion analyses were performed using a J-SCIENCE LAB JM10. Unless otherwise noted, materials were purchased from Tokyo Chemical Industry Co., Ltd. (Japan), Aldrich Inc. (U.S.A.), Wako Pure Chemical Industries, Ltd. (Osaka, Japan), Nacalai Tesque Inc., Kanto Chemical Co., Inc. (Japan) commercial suppliers and were used as purchased. For manganese(IV) oxide, Wako manganese(IV) oxide, powder (order number 138-09675) was used. The substrates **1p**,[35] **r**[36] and catalyst **3**[34] were prepared according to the literature procedure.

Synthesis of the *N*-PMP Glycine Derivatives

Ethyl (4-Methoxyphenyl)glycinate (**1a**)

To a solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in CH_3CN (25 mL) were added NaOAc (1.23 g, 15.0 mmol), NaI (1.65 g, 11.0 mmol) and *p*-anisidine (1.19 g, 9.66 mmol) at room temperature and stirred at the same temperature for 3 h. After that, the reaction mixture was extracted wih EtOAc, washed with 5% $KHSO_{4aq}$ and brine, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane–EtOAc=4 : 1) to afford **1a** (1.47 g, 73%) as a pale brown plate crystal. mp 44–45°C (hexane–EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, *J*=7.0 Hz, 3H), 3.75 (s, 3H), 3.86 (s, 2H), 4.02 (s, 1H), 4.23 (q, *J*=7.0 Hz, 2H), 6.59 (d, *J*=9.0 Hz, 2H), 6.79 (d, *J*=9.0 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 14.2, 46.8, 55.7, 61.2, 114.3, 114.9, 141.2, 152.6, 171.3; IR (neat) 826, 1443, 1518, 1732, 2992, 3385 cm^{-1}; MS (ESI$^+$) *m*/*z* 210 (M+H$^+$, 100); *Anal*. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.94; H, 7.20; N, 6.77.

Methyl (4-Methoxyphenyl)glycinate (**1b**)

To a solution of *p*-anisidine (10.2 g, 82.8 mmol) in CH_3CN (100 mL) were added K_2CO_3 (12.3 g, 89.0 mmol) and methyl bromoacetate (8.25 mL, 89.0 mmol) at room temperature and stirred at the same temperature for 10 h. After that, the insolubilities were removed by filtration. Then the resulting filtrate was evaporated *in vacuo* and purified by silica gel column chromatography (hexane–EtOAc=4 : 1 to 2 : 1) to afford **1b** (11.7 g, 72%) as a pale brown plate crystal. mp 79–80°C

(hexane–EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 3.77 (s, 3H), 3.88 (s, 2H), 4.01 (s, 1H), 6.59 (d, J=9.0 Hz, 2H), 6.79 (d, J=9.0 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 46.4, 52.0, 55.5, 114.2, 114.7, 141.1, 152.5, 171.8; IR (KBr) 1440, 1524, 1746, 3410 cm^{-1}; MS (ESI$^+$) m/z 196 (M+H$^+$, 100); *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.40; H, 6.69; N, 7.02.

tert-Butyl (4-Methoxyphenyl)glycinate (**1c**)

A procedure similar to that described for the preparation of **1b** afforded **1c** in 92% yield as an yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.46 (s, 9H) 3.71 (s, 3H), 3.73 (s, 2H), 4.02 (s, 1H), 6.55 (d, J=8.9 Hz, 2H), 6.76 (d, J=8.9 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 27.9, 47.3, 55.5, 81.5, 114.1, 114.7, 141.4, 152.3, 170.4; IR (neat) 1462, 1506, 1731, 2980, 3381 cm^{-1}; MS (ESI$^+$) m/z 238 (M+H$^+$, 100); high resolution (HR)-MS (ESI$^+$) m/z Calcd for $C_{13}H_{20}NO_3$ ([M+H]$^+$) 238.1438. Found 238.1444.

Benzyl (4-Methoxyphenyl)glycinate (**1d**)

A procedure similar to that described for the preparation of **1b** afforded **1d** in 92% yield as a white needle crystal. mp 73–74°C (hexane–EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.73 (s, 3H) 3.91 (s, 2H), 4.04 (s, 1H), 5.19 (s, 2H), 6.57 (d, J=8.8 Hz, 2H), 6.77 (d, J=8.8 Hz, 2H), 7.31-7.38 (m, 5H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 46.9, 55.7, 66.9, 114.4, 114.9, 128.3, 128.4, 128.6, 135.3, 141.1, 152.7, 171.3; IR (KBr) 757, 797, 1451, 1464, 1518, 1728, 3388 cm^{-1}; MS (ESI$^+$) m/z 272 (M+H$^+$, 100); *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.72; H, 6.26; N, 5.07.

Allyl (4-Methoxyphenyl)glycinate (**1e**)

A procedure similar to that described for the preparation of **1b** afforded **1e** in 92% yield as an yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.72 (s, 3H), 3.88 (s, 2H), 4.04 (s, 1H), 4.64 (ddd, J_1=4.6 Hz, J_2=1.5 Hz, J_3=1.3 Hz, 2H), 5.24 (dt, J_1=10.4 Hz, J_2=1.3 Hz, 1H), 5.31 (dt, J_1=17.2 Hz, J_2=1.5 Hz, 1H), 5.90 (ddt, J_1=17.2 Hz, J_2=10.4 Hz, J_3=4.6 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 6.77 (d, J=8.8 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 46.6, 55.6, 65.6, 114.2, 114.8, 118.7, 131.6, 141.1, 152.5, 171.0; IR (neat) 937, 987, 1444, 1516, 1744, 3031, 3389 cm^{-1}; MS (ESI$^+$) m/z 222 (M+H$^+$, 100); HR-MS (ESI$^+$) m/z Calcd for $C_{12}H_{15}NNaO_3$ ([M+Na]$^+$) 244.0944. Found 244.0938.

Ethyl (4-Methoxyphenyl)glycylglycinate (**1f**)

To a suspension of ethylglycinate hydrochloride (3.58 g, 25.6 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (10.7 mL, 76.9 mmol) and chloroacetyl chloride (3.05 mL, 38.4 mmol) at 0°C and stirred at room temperature for 20 min. After that, sat. $NaHCO_{3aq}$ was added at 0°C and the reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated *in vacuo* to afford the chloroacetamide intermediate as a dark black solid. This intermediate was directly used for the next step without further purifications.

To a solution of chloroacetamide in CH_3CN (50 mL) were added *p*-anisidine (4.90 g, 39.8 mmol), K_2CO_3 (4.04 g, 29.2 mmol) and KI (4.25 g, 25.6 mmol) at room temperature and stirred at the same temperature for 24 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane–EtOAc=1 : 1 to 1 : 2) to afford **1f** (3.21 g, 47% in two steps) as a pale brown powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.3 Hz, 3H), 3.74 (s, 3H), 3.78 (s, 2H), 4.04 (d, J=5.5 Hz, 2H), 4.12 (s, 1H), 4.17 (q, J=7.3 Hz, 2H), 6.59 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H), 7.31 (t, J=5.5 Hz, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 14.0, 40.9, 49.5, 55.6, 61.4, 114.4, 114.9, 141.1, 153.1, 169.6, 171.3; IR (KBr) 1422, 1441, 1450, 1589, 1621, 1655, 2969, 3363 cm^{-1}; MS (ESI$^+$) m/z 267 (M+H$^+$, 75), 289 (M+Na$^+$, 100); *Anal.* Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.44; H, 6.81; N, 10.32.

N-Ethyl-2-((4-methoxyphenyl)amino)-*N*-phenylacetamide (**1g**)

A procedure similar to that described for the preparation of **1f** afforded **1g** in 42% yield as a white needle crystal. mp 118–119°C (hexane–EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.15 (t, J=7.3 Hz, 3H), 3.47 (s, 2H), 3.71, (s, 3H), 3.80 (q, J=7.3 Hz, 2H), 4.48 (s, 1H), 6.41 (d, J=9.0 Hz, 2H), 6.71 (d, J=9.0 Hz, 2H), 7.17–7.22 (m, 2H), 7.40–7.51 (m, 3H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 12.9, 44.3, 47.1, 55.7, 114.1, 114.7, 128.2, 128.4, 129.9, 140.6, 141.7, 152.1, 169.0; IR (KBr) 1423, 1461, 1518, 1535, 1653, 2980, 3394 cm^{-1}; MS (ESI$^+$) m/z 285 (M+H$^+$, 100); *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.69; H, 7.13; N, 9.70.

N-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)glycine

To a solution of **1a** (5.04 g, 25.8 mmol) in EtOH (100 mL) were added Na_2CO_3 (5.60 g, 52.8 mmol) and Boc_2O (11.5 g, 52.7 mmol) at room temperature and stirred at 80°C. After 2 h, Boc_2O (5.13 g, 23.5 mmol) was added at room temperature and stirred at 80°C for 1 h. Then the reaction mixture was cooled to 0°C, evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude Boc-protected product as yellow oil. This crude intermediate was directly used for the next transformation.

To a solution of crude Boc-protected intermediate in MeOH (25 mL) was added 2 M $NaOH_{aq}$ (25 mL) at room temperature and stirred at the same temperature for 90 min. Then the reaction mixture was evaporated *in vacuo*, washed with $CHCl_3$, acidified with 5% $KHSO_{4aq}$, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford *N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxyphenyl)glycine as a white powder. ^{1}H-NMR (300 MHz, DMSO-d_6, 40°C) δ: 1.35 (s, 9H), 3.73 (s, 3H), 4.13 (s, 2H), 6.87 (d, J=8.6 Hz, 2H), 7.17 (d, J=8.6 Hz, 2H), 12.6 (s, 1H); ^{13}C-NMR (75.0 MHz, DMSO-d_6) δ: 27.7, 51.9, 55.1, 79.5, 113.6, 127.4, 135.55, 135.59, 153.8, 157.0; IR (KBr) 1415, 1513, 1668, 1769, 3142 cm^{-1}; MS (ESI$^+$) m/z 304 (M+Na$^+$, 100); *Anal.* Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.62; H, 6.75; N, 4.90.

Phenyl (4-Methoxyphenyl)glycinate (**1h**)

To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxyphenyl)glycine (519 mg, 1.84 mmol) in CH_2Cl_2 (9.2 mL) were added DMAP (22.4 mg, 0.18 mmol), PhOH (324 μL, 3.68 mmol) and EDCI·HCl (936 mg, 5.23 mmol) at 0°C and stirred at room temperature. After 0.5 h, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude phenyl ester as colorless oil. This product was used for the next step without further purification.

To a solution of crude phenyl ester in CH_2Cl_2 (15.6 mL) was added TFA (1.56 mL) at 0°C and stirred at room temperature for 1 h. Then, the reaction mixture was cooled to 0°C, basified to pH 8 with sat.$NaHCO_{3aq}$, extracted with $CHCl_3$, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane–EtOAc=3 : 1) to afford **1h** (284 mg, 60% over two steps) as a pale brown powder. mp 118–119°C (hexane–EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.76 (s, 3H),

4.09 (s, 1H), 4.14 (s, 2H), 6.66 (d, J=9.0 Hz, 2H), 6.82 (d, J=9.0 Hz, 2H), 7.08 (d, J=7.5 Hz, 2H), 7.24 (dd, J_1=J_2=7.5 Hz, 1H), 7.38 (dd, J_1=J_2=7.5 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 47.0, 55.7, 114.5, 114.9, 121.3, 126.1, 129.5, 141.0, 150.3, 152.8, 170.1; IR (KBr) 821, 1441, 1517, 1749, 3403 cm^{-1}; MS (ESI$^+$) m/z 258 (M+H$^+$, 52), 280 (M+Na$^+$, 100); *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.93; H, 5.85; N, 5.67.

2,2,2-Trifluoroethyl (4-Methoxyphenyl)glycinate (**1i**)

A procedure similar to that described for the preparation of **1h** afforded **1i** in 82% yield as an yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 4.00 (s, 2H), 4.54 (q, J=8.3 Hz, 2H), 6.58 (dd, J_1=8.8 Hz, J_2=2.3 Hz, 2H), 6.79 (dd, J_1=8.8 Hz, J_2=2.3 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 46.2, 55.5, 60.5 (q, J=36.5 Hz),114.4, 114.8, 122.7 (q, J=275.0 Hz), 140.7, 152.8, 170.1; IR (neat) 1423, 1445, 1517, 1766, 3393 cm^{-1}; MS (ESI$^+$) m/z 264 (M+H$^+$, 100), 286 (M+Na$^+$, 75); HR-MS (ESI$^+$) m/z Calcd for $C_{11}H_{13}F_3NO_3$ ([M+H]$^+$) 264.0842. Found 264.0836.

1,1,1,3,3,3-Hexafluoropropan-2-yl (4-Methoxyphenyl)glycinate (**1j**)

A procedure similar to that described for the preparation of **1h** afforded **1j** in 82% yield as an yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 4.13 (s, 2H), 5.80 (hept, J=6.0 Hz, 1H), 6.58 (dd, J_1=9.0 Hz, J_2=2.2 Hz, 2H), 6.80 (dd, J_1=9.0 Hz, J_2=2.2 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 46.2, 55.7, 66.9 (hept, J=34.6 Hz), 114.5, 115.0, 120.2 (q, J=281.2 Hz), 140.1, 153.2, 168.9; IR (KBr) 1386, 1519, 1789, 3397 cm^{-1}; HR-MS (ESI$^+$) m/z Calcd for $C_{12}H_{12}F_6NO_3$ ([M+H]$^+$) 332.0716. Found 332.0717.

1-((4-Methoxyphenyl)glycyl)pyrrolidin-2-one (**1k**)

To a solution of pyrrolidin-2-one (630 mg, 7.40 mmol) in CH_3CN (20 mL) were added pyridine (1.19 mL, 14.8 mmol) and bromoacetyl bromide (1.29 mL, 14.8 mmol) at 0°C and stirred at room temperature for 52 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* to afford the bromoacetimide intermediate as a brown oil. This intermediate was directly used for the next step without further purifications.

To a solution of bromoacetimide in CH_3CN (20 mL) were added *p*-anisidine (1.12 g, 9.09 mmol), K_2CO_3 (1.54 g, 11.1 mmol) and KI (2.11 g, 12.7 mmol) at room temperature and stirred at the same temperature for 18 h. After that, the reaction mixture was extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane–EtOAc=2 : 1 to 1 : 1) to afford **1k** (900 mg, 49% in two steps) an yellow powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.11 (tt, J_1=8.1 Hz, J_2=7.1 Hz, 2H), 2.64 (t, J=8.1 Hz, 2H), 3.74 (s, 3H), 3.86 (t, J=7.1 Hz, 2H), 4.42 (s, 2H), 4.50 (s, 1H), 6.65 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 17.6, 33.2, 45.2, 50.1, 55.7, 114.4, 114.9, 141.4, 152.4, 171.6, 175.4; IR (KBr) 1420, 1515, 1690, 1727, 3385 cm^{-1}; MS (ESI$^+$) m/z 249 (M+H$^+$, 100); *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.23; H, 6.47; N, 11.16.

N-((4-Methoxyphenyl)glycyl)benzamide (**1l**)

A mixture of benzamide (2.94 g, 24.3 mmol) and chloroacetyl chloride (2.32 mL, 29.1 mmol) was stirred at 110°C for 45 min. After that, the reaction mixture was evaporated *in vacuo* to remove the volatile by-products. The resulting residue was added Et_2O and the precipitate was crashed. Then, the supernatant was discarded. This process was repeated six times to afford the crude chloroacetimide. This intermediate was directly used for the next step without further purifications.

To a solution of chloroacetimide in CH_3CN (100 mL) were added *p*-anisidine (3.13 g, 25.4 mmol), K_2CO_3 (3.56 g, 25.8 mmol) and KI (3.24 g, 19.5 mmol) at room temperature and stirred at the same temperature for 13 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and the resulting brown solid was purified by recrystallization from hexane and EtOAc to afford **1l** (4.45 g, 64% in two steps) as an yellow powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 4.36 (s, 1H), 4.40 (s, 2H), 6.69 (d, J=8.8 Hz, 2H), 6.82 (d, J=8.8 Hz, 2H), 7.49 (dd, J_1=J_2=7.4 Hz, 2H), 7.62 (dd, J_1=J_2=7.4 Hz, 1H), 7.81 (d, J=7.4 Hz, 2H), 9.13 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 50.8, 55.7, 114.6, 115.0, 127.7, 128.9, 132.3, 133.3, 141.0, 152.8, 165.4, 173.2; IR (KBr) 727, 1424, 1520, 1731, 3280, 3272 cm^{-1}; MS (ESI$^+$) m/z 285.3 (M+H$^+$, 100); *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.29; H, 5.64; N, 9.67.

S-Benzyl 2-((4-Methoxyphenyl)amino)ethanethioate (**1m**)

A procedure similar to that described for the preparation of **1h** afforded **1m** in 52% yield as a white powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 4.02 (s, 2H), 4.11 (s, 2H), 6.56 (d, J=9.0 Hz, 2H), 6.78 (d, J=9.0 Hz, 2H), 7.19–7.32 (m, 5H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 32.8, 55.0, 55.7, 114.1, 114.9, 127.3, 128.6, 128.8, 137.3, 140.7, 152.8, 200.6; IR (KBr) 823, 1436, 1459, 1515, 1682, 3399 cm^{-1}; MS (ESI$^+$) m/z 288 (M+H$^+$, 97), 310 (M+Na$^+$, 100); *Anal.* Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.57; H, 5.81; N, 4.81.

Methyl (2-Methoxyphenyl)glycinate (**1o**)

A procedure similar to that described for the preparation of **1a** afforded **1o** in 32% yield as a colorless oil. The spectral data were identical to that described in the literature.[37]

Methyl Tritylglycinate (**1s**)

To a solution of methylglycinate hydrochloride (1.26 g, 10.0 mmol) in *N*,*N*-dimethylformamide (DMF) (20 mL) were added Et_3N (3.50 mL, 25.1 mmol) and chlorotriphenylmethane (2.90 g, 10.4 mmol) at 0°C. After stirring the resulting white suspension at room temperature for 19 h, the reaction was added H_2O, extracted with EtOAc–hexane (2 : 1), dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane–EtOAc=4 : 1) to afford **1s** (2.74 g, 83%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.21 (s, 2H), 3.65 (s, 3H), 7.23–7.26 (m, 3H), 7.32–7.35 (m, 6H), 7.53–7.55 (m, 6H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 45.7, 51.7, 70.7, 126.5, 127.9, 128.6, 145.3, 172.6 cm^{-1}; IR (neat) 706, 1491, 1742, 3330 cm^{-1}; HR-MS (ESI$^+$) m/z Calcd for $C_{22}H_{21}NO_2$ ([M+Na] $^+$) 354.1465. Found 354.1470.

MnO_2-Mediated Oxidation of 1

Ethyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2a**)

To a solution of **1a** (209 mg, 1.00 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (740 mg, 20.0 mmol) at room temperature and stirred at room temperature for 1 h. Then, the reaction mixture was passed through Celite and the filtrate was evaporated *in vacuo* to afford the corresponding imine **2a** (193 mg, 93%) as a red oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, J=7.3 Hz, 3H), 3.84 (s, 3H), 4.42 (q, J=7.3 Hz, 2H), 6.94 (d, J=9.0 Hz, 2H), 7.36 (d, J=9.0 Hz, 2H), 7.94 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 14.2, 55.5, 61.9, 114.5, 123.6,

141.3, 147.9, 160.5, 163.6; IR (neat) 1506, 1585, 1713, 1741, 2987 cm^{-1}; MS (ESI$^+$) *m/z* 208 (M+H$^+$, 13), 230 (M+Na$^+$, 100); HR-MS (ESI$^+$) *m/z* Calcd for $C_{11}H_{14}NO_3$ ([M+H]$^+$) 208.0968. Found 208.0973.

Methyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2b**)

A procedure similar to that described for the preparation of **2a** afforded **2b** in 92% yield as a red oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 3.95 (s, 3H), 6.94 (d, J=8.8 Hz, 2H), 7.37 (d, J=8.8 Hz, 2H), 7.95 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 52.8, 55.5, 114.5, 123.6, 141.1, 147.3, 160.6, 164.1; IR (neat) 1507, 1585, 1715, 1743 cm^{-1}; MS (ESI$^+$) *m/z* 194 (M+H$^+$, 15), 216 (M+Na$^+$, 100); HR-MS (ESI$^+$) *m/z* Calcd for $C_{10}H_{12}NO_3$ ([M+H]$^+$) 194.0812. Found 194.0814.

tert-Butyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2c**)

A procedure similar to that described for the preparation of **2a** afforded **2c** in 98% yield as a red oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.59 (s, 9H), 3.83 (s, 3H), 6.92 (d, J=9.0 Hz, 2H), 7.33 (d, J=9.0 Hz, 2H), 7.86 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 27.9, 55.4, 82.7, 114.3, 123.4, 136.4, 141.6, 149.4, 160.2, 162.8; IR (neat) 1506, 1593, 1710, 1733, 2980 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{13}H_{18}NO_3$ ([M+H]$^+$) 236.1281. Found 236.1289.

Benzyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2d**)

A procedure similar to that described for the preparation of **2a** afforded **2d** in 90% yield as a red oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 5.38 (s, 2H), 6.93 (d, J=9.0 Hz, 2H), 7.34–7.42 (m, 5H), 7.44–7.48 (m, 2H), 7.97 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 55.5, 67.4, 114.5, 123.6, 128.5, 128.59, 128.62, 135.2, 141.3, 147.5, 160.6, 163.3; IR (neat) 836, 1459, 1510, 1585, 1715, 1741 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{16}H_{16}NO_3$ ([M+H]$^+$) 270.1125. Found 270.1142.

Allyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2e**)

A procedure similar to that described for the preparation of **2a** afforded **2e** in 87% yield as a red oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 4.84 (ddd, J_1=6.0 Hz, J_2=J_3=1.2 Hz, 2H), 5.32 (ddd, J_1=10.3 Hz, J_2=J_3=1.2 Hz, 1H), 5.43 (ddd, J_1=16.0 Hz, J_2=J_3=1.2 Hz, 1H), 6.03 (ddd, J_1=16.0 Hz, J_2=10.3 Hz, J_3=6.0 Hz, 1H), 6.89 (d, J=9.0 Hz, 2H), 7.37 (d, J=9.0 Hz, 2H), 7.97 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 55.4, 66.3, 114.5, 119.4, 123.6, 131.4, 136.5, 141.2, 147.4, 160.6, 163.2; IR (neat) 935, 990, 1463, 1506, 1585, 1727, 1743, 3367 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{12}H_{14}NO_3$ ([M+H]$^+$) 220.0968. Found 220.0976.

Ethyl (*E*)-(2-((4-Methoxyphenyl)imino)acetyl)glycinate (**2f**)

A procedure similar to that described for the preparation of **2a** afforded **2f** in 95% yield as a red solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, J=7.1 Hz, 3H), 4.18 (d, J=5.5 Hz, 2H), 3.64 (s, 3H), 4.26 (q, J=7.1 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.30 (d, J=8.8 Hz, 2H), 7.70 (s, 1H), 7.89 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 14.0, 40.9, 55.3, 61.4, 114.4, 123.4, 140.2, 149.4, 160.1, 163.8, 169.4; IR (neat) 1464, 1506, 1593, 1680, 1752, 2982, 3382 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{13}H_{17}N_2O_4$ ([M+H]$^+$): 265.1183. Found 265.1188.

(*E*)-*N*-Ethyl-2-((4-methoxyphenyl)imino)-*N*-phenylacetamide (**2g**)

A procedure similar to that described for the preparation of **2a** afforded **2g** in 99% yield as a red solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.22 (t, J=7.3 Hz, 3H), 3.77 (s, 3H), 3.95 (q, J=7.3 Hz, 2H), 6.81 (d, J=8.8 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 7.24 (d, J=7.3 Hz, 2H), 7.38 (dd, J_1=J_2=7.3 Hz, 1H), 7.44 (dd, J_1=J_2=7.3 Hz, 2H), 7.73 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 12.7, 44.7, 55.3, 114.1, 122.8, 127.9, 128.2, 129.6, 136.4, 140.5, 142.5, 150.7, 159.1, 162.6; IR (neat) 835, 1458, 1498, 1593, 1626, 1662, 2979 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{17}H_{19}N_2O_2$ ([M+H]$^+$) 283.1441. Found 283.1455.

Phenyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2h**)

A procedure similar to that described for the preparation of **2a** afforded **2h** in 92% yield as a red solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 6.98 (d, J=9.0 Hz, 2H), 7.23–7.31 (m, 3H), 7.40–7.46 (m, 4H), 8.14 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 55.5, 114.6, 121.4, 123.9, 126.2, 129.5, 141.0, 146.7, 150.5, 160.9, 162.0; IR (neat) 837, 1509, 1585, 1733, 1759 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{15}H_{14}NO_3$ ([M+H]$^+$) 256.0968. Found 256.0963.

2,2,2-Trifluoroethyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (**2i**)

A procedure similar to that described for the preparation of **2a** afforded **2i** in 98% yield as a red solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 4.72 (q, J=8.3 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 7.42 (d, J=9.0 Hz, 2H), 8.02 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 55.5, 61.0 (q, J=36.4 Hz), 114.6, 122.7 (q, J=275.0 Hz), 124.0, 136.5, 140.7, 145.0, 161.1, 161.6; IR (neat) 1443, 1507, 1585, 1738, 1763 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{11}H_{11}F_3NO_3$ ([M+H]$^+$) 262.0686. Found 262.0698.

1,1,1,3,3,3-Hexafluoropropan-2-yl (*E*)-2-((4-Methoxyphenyl)-imino)acetate (**2j**)

A procedure similar to that described for the preparation of **2a** afforded **2j** in 88% yield as a red solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 5.98 (hept, J=6.0 Hz, 1H), 6.96 (d, J=9.0 Hz, 2H), 7.46 (d, J=9.0 Hz, 2H), 8.07 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 55.5, 67.2 (hept, J=35.2 Hz), 114.7, 120.3 (q, J=280.0 Hz), 124.4, 140.4, 142.9, 159.9, 161.7; IR (neat) 1512, 1579, 1748, 1783 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{12}H_{10}F_6NO_3$ ([M+H]$^+$): 330.0559. Found 330.0556.

(*E*)-1-(2-((4-Methoxyphenyl)imino)acetyl)pyrrolidin-2-one (**2k**)

A procedure similar to that described for the preparation of **2a** afforded **2k** in 96% yield as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.18 (tt, J_1=8.3 Hz, J_2=7.3 Hz, 2H), 2.68 (t, J=8.3 Hz, 2H), 3.97 (t, J=7.3 Hz, 2H), 3.84 (s, 3H), 6.93 (d, J=9.0 Hz, 2H), 7.42 (d, J=9.0 Hz, 2H), 8.86 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 17.7, 32.9, 45.1, 55.4, 114.3, 123.6, 142.2, 150.6, 160.1, 163.7, 176.0; IR (neat) 1508, 1580, 1691, 1741 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{13}H_{14}N_2NaO_3$ ([M+Na]$^+$) 269.0897. Found 269.0892.

(*E*)-*N*-(2-((4-Methoxyphenyl)imino)acetyl)benzamide (**2l**)

A procedure similar to that described for the preparation of **2a** afforded **2l** in 91% yield as a red solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 6.96 (dd, J_1=2.0, J_2=2.2 Hz 2H), 7.39 (dd, J_1=2.2, J_2=2.0 Hz, 2H), 7.60–7.63 (m, 1H), 7.92 (d, J=1.5 Hz, 1H), 7.93 (br, 2H), 10.59 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 55.5, 114.7, 127.7, 128.9, 133.1, 138.8, 148.3, 161.2, 161.4, 164.3; IR (neat) 837, 1504, 1579, 1682, 1743, 3354 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{16}H_{15}N_2O_3$ ([M+H]$^+$): 283.1077. Found 283.1085.

S-Benzyl (*E*)-2-((4-Methoxyphenyl)imino)ethanethioate (**2m**)

A procedure similar to that described for the preparation of **2a** afforded **2m** in quantitative yield as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 4.23 (s, 2H), 6.93 (d, J=9.0 Hz, 2H), 7.22–7.38 (m, 7H), 8.02 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ: 32.6, 55.5, 114.6, 124.1, 127.3, 128.6, 129.0, 137.2, 140.3, 151.0, 160.8, 191.9; IR (neat) 838,

1457, 1505, 1583, 1659 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{16}H_{16}NO_2S$ ([M+H]$^+$) 286.0896. Found 286.0903.

Asymmetric Mannich Reaction of α-Imino Carboxylic Acid Derivatives

Ethyl 1-(1-((4-Methoxyphenyl)amino)-2-oxo-2-(2-oxopyrrolidin-1-yl)ethyl)-2-oxocyclopentane-1-carboxylate (**5e**)

A mixture of **2k** (18.4 mg, 0.0747 mmol), thiourea **3** (3.0 mg, 0.00726 mmol) and cyclopentanone-2-carboxylic acid ethyl ester **4** (21.6 μL, 0.149 mmol) in toluene (0.75 mL) was stirred at room temperature for 24 h. Then, the reaction mixture was directly purified by silica gel column chromatography (hexane–EtOAc=2 : 1 to 1 : 1) to afford the desired Mannich adduct **5e** (23.1 mg, 77%, dr=61 : 39) as a brown oil. HPLC [Chiralpak IA, hexane–2-propanol=90 : 10, 1.0 mL/min, λ=254 nm, retention times: (major) 57.5 min (minor) 53.4 min, 92% enantiomeric excess (ee) and (major) 63.4 min (minor) 43.5 min, 52% ee]; $[\alpha]_D^{23}$ +9.2 (c=0.94 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) (mixture of diastereomers, with signals corresponding to the one of them indicated by) δ: 1.24 (t, J=9.5 Hz, 3H), 1.89–2.10 (m, 4H), 2.23–2.48 (m, 3H), 2.51–2.71 (m, 3H), 3.70–3.84 (m, 5H), 4.07–4.20 (m, 3H), 6.35 (s, 1H), 6.71–6.74 (m, 2H), 6.77–6.82 (m, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) (mixture of diastereomers) δ: 13.9, 14.0, 17.0, 17.1, 19.6, 19.8, 30.0, 33.0, 33.6, 33.7, 38.2, 38.4, 45.77, 45.82, 55.6, 55.8, 58.9, 59.2, 61.8, 62.1, 62.5, 64.7, 114.6, 114.8, 116.7, 117.0, 139.9, 140.3, 153.2, 153.4, 168.5, 170.9, 172.7, 173.2, 175.3, 175.8, 212.1, 212.3; IR (neat) 1463, 1513, 1690, 1745, 2982, 3363 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{21}H_{27}N_2O_6$ ([M+H]$^+$) 403.1864. Found 403.1862.

Ethyl 1-(2-Ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclopentane-1-carboxylate (**5a**)

A procedure similar to that described for the preparation of **5e** afforded **5a** in 25% yield as pale yellow oil. (dr=57 : 43). HPLC [Chiralpak IC-3, hexane–2-propanol=95 : 5, 1.0 mL/min, λ=254 nm, retention times: (major) 63.6 min, (minor) 54.7 min, 84% ee and (major) 47.1 min, (minor) 35.4 min, 36% ee]; $[\alpha]_D^{20}$ +0.15 (c=0.58 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) (mixture of diastereomers, with signals corresponding to the one of them indicated by) δ: 1.15–1.27 (m, 6H), 1.97–1.98 (m, 2H), 2.12–2.33 (m, 2H), 2.38–2.55 (m, 2H), 3.72 (s, 3H), 4.10–4.20 (m, 4H), 4.66–4.73 (m, 1H), 6.59–6.81 (m, 4H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) (mixture of diastereomers) δ: 13.9, 14.0, 19.3, 19.8, 29.8, 30.9, 37.6, 38.7, 55.6, 61.1, 61.4, 61.7, 61.8, 62.5, 64.7, 114.5, 114.6, 115.9, 116.8, 140.8, 141.5, 153.2, 168.8, 169.4, 171.5, 171.6, 211.8, 212.3; IR (neat) 827, 1514, 1724, 2981, 3362 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{19}H_{26}NO_6$ ([M+H]$^+$) 364.1755. Found 364.1743.

Ethyl 1-(1-((4-Methoxyphenyl)amino)-2-oxo-2-phenoxyethyl)-2-oxocyclopentane-1-carboxylate (**5b**)

A procedure similar to that described for the preparation of **5e** afforded **5b** in 31% yield as pale yellow oil. (dr=51 : 49). HPLC [Chiralpak IB-3, hexane–2-propanol=90 : 10, 1.0 mL/min, λ=254 nm, retention times: (major) 15.3 min, (minor) 11.6 min, 51% ee and (major) 13.6 min, (minor) 17.2 min, 7% ee]; $[\alpha]_D^{20}$ −11.1 (c=0.86 in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of diastereomers, with signals corresponding to the one of them indicated by) δ: 1.10–1.21 (m, 3H), 1.86–2.04 (m, 2H), 2.13–2.60 (m, 4H), 3.68 (s, 3H), 4.09–4.17 (m, 2H), 4.79 (s, 1H), 6.69–6.74 (m, 3H), 6.79–6.81 (m, 1H), 6.87–6.89 (m, 1H), 7.00–7.01 (m, 1H), 7.11–7.16 (m, 1H), 7.23–7.29 (m, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) (mixture of diastereomers) δ: 14.0, 19.4, 19.9, 30.2, 31.6, 37.5, 38.6, 55.6, 55.7, 61.4, 62.09, 62.12, 62.5, 62.6, 65.0, 114.7, 114.8, 116.2, 117.3, 121.2, 121.3, 126.1, 126.2, 129.4, 140.3, 150.2, 150.4, 153.7, 153.9, 169.1, 169.9, 170.3, 170.4, 212.3, 212.6; IR (neat) 825, 1463, 1514, 1724, 1753, 2980, 3368 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{23}H_{26}NO_6$ ([M+H]$^+$) 412.1755. Found 412.1749.

Ethyl 1-(2-(Benzylthio)-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclopentane-1-carboxylate (**5g**)

A procedure similar to that described for the preparation of **5e** afforded **5g** in 40% yield as pale yellow oil. (dr=51 : 49). HPLC [Chiralpak IC-3, hexane–2-propanol=97/3, 1.0 mL/min, λ=254 nm, retention times: (major) 75.3 min, (minor) 85.5 min, 82% ee and (major) 93.9 min, (minor) 57.9 min, 56% ee]; $[\alpha]_D^{23}$ −66.4 (c=0.45 in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of diastereomers, with signals corresponding to the one of them indicated by) δ: 1.00 (t, J=7.0 Hz, 3H), 1.84–1.94 (m, 3H), 2.12–2.54 (m, 4H), 3.66 (s, 3H), 3.89–4.06 (m, 4H), 4.79 (s, 1H), 6.59–6.70 (m, 4H), 7.11–7.21 (m, 5H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) (mixture of diastereomers) δ: 13.7, 13.9 19.4, 19.8, 29.4, 30.4, 33.5, 33.8, 37.7, 38.7, 55.57, 55.61, 62.0, 62.1, 62.7, 65.0, 67.8, 67.9, 114.7, 114.8, 115.1, 115.7, 127.2, 127.3, 128.5, 128.8, 128.9, 136.9, 137.1, 139.8, 140.0, 153.2, 153.3, 168.3, 169.0, 199.9, 202.0, 210.6, 213.4; IR (neat) 824, 1460, 1514, 1679, 1724, 1752, 2980, 3382 cm^{-1}; HR-MS (ESI$^+$) *m/z* Calcd for $C_{24}H_{28}NO_5S$ ([M+H]$^+$) 442.1683. Found 442.1676.

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