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A convenient method for the preparation of chiral phosphonoacetamides and their Horner–Wadsworth–Emmons reaction

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Abstract—Chiral phosphonoacetamides bearing (*S*)-(α-methylbenzyl)benzylamine, (*S*,*S*)-bis(α-methylbenzyl)amine, L-phenylglycine methyl ester and L-phenylglycinol were easily prepared in good yield by means of the Michaelis–Arbuzov reaction of chiral bromoacetamides obtained in quantitative yield, with trimethyl phosphite, which under Horner–Wadsworth–Emmons conditions with several aryl and alkyl aldehydes under Masamune–Roush procedure using LiCl and DBU in THF or toluene gave the corresponding chiral α,β-unsaturated amides. The present procedure is a convenient and efficient methodology for the preparation of phosphonoacetamides and chiral α,β-unsaturated amides in high *E*-selectivity.

1. Introduction

The stereodefined synthesis of carbon–carbon double bonds with high selectivity is critically important in organic synthesis, since geometrically-defined olefins serve as good building blocks in organic synthesis.[1] Of particular utility are the olefins bearing electron-withdrawing groups, such as the carbonyl group, since these groups are not only viable for further functionalization, but they also activate the olefin moiety for reactions such as Michael addition[2] and cycloaddition reactions.[3] Additionally, α,β-unsaturated amides belong to an important class of natural products, which show both biological[4] and insecticide activities.[5] For these reasons, the preparation of α,β-unsaturated amides is a topic of great interest, in this context the Wittig reaction and related reactions have served as the most powerful method for the construction of double bonds.[6] The Horner–Wadsworth–Emmons (HWE) modification of the Wittig reaction in particular is widely employed.[7,8] The reactions of aldehydes with phosphonates bearing α-substituents that stabilize the carbanion preferentially furnish the corresponding *E*-alkenes. Recently, we described the highly selective synthesis of chiral (*E*)-α,β-unsaturated amides bearing (*S*)-α-methylbenzylamine from phosphonoacetamides via a HWE reaction.[9] As an extension of this methodology, in this work we herein report the synthesis of several chiral α,β-unsaturated amides bearing (*S*)-(α-methylbenzyl)benzylamine,[10] (*S*,*S*)-bis(α-methylbenzyl)amine,[11] (*S*)-phenylglycine methyl ester[12] and (*S*)-phenylglycinol[13] via a HWE reaction from the corresponding phosphonoacetamides **4**–**8**.

2. Results and discussion

The starting chiral phosphonoacetamides **4**–**6** were easily prepared by employing the protocol recently developed in our laboratories.[14] In this context, the treatment of the appropriate chiral amine[15] with bromoacetyl bromide in the presence of K_2CO_3 in a CH_2Cl_2/H_2O mixture at room temperature, afforded the corresponding chiral α-bromo-

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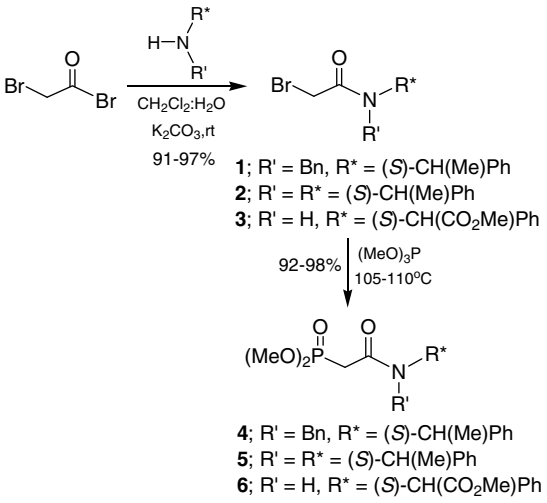
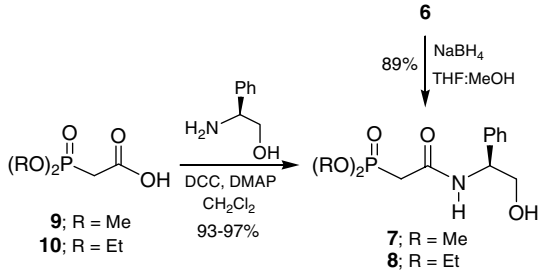
acetamides **1**–**3** in excellent yields,[16] which by means of the Michaelis–Arbuzov reaction[17] with trimethyl phosphite gave the chiral phosphonoacetamides **4**–**6** in 92–98% yield (Scheme 1).[18]



Scheme 1.

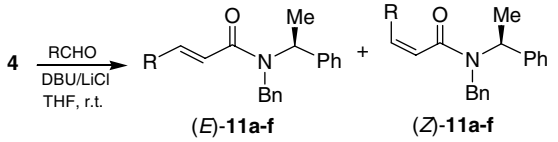
On the other hand, reduction of the methyl ester group in phosphonoacetamide **6** with sodium borohydride in THF/MeOH at reflux[19] produced phosphonoacetamide **7** in 89% yield. Additionally, treatment of phosphonoacetic acid **9**, obtained by hydrolysis from the corresponding ethyl ester derivative, with L-phenylglycinol[20] in the presence of dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane at room temperature, afforded phosphonoacetamide **7** in 97% yield. In a similar manner, **8** was obtained in 93% yield from the corresponding phosphonoacetic acid **10** (Scheme 2).[21]



Scheme 2.

With phosphonoacetamides **4**–**8** in hand, we initiated our own investigation by examining the HWE reaction of **4**–**8** with several aryl and alkyl aldehydes to obtain the corresponding chiral α,β-unsaturated amides. Thus, in the first instance and following the Masamune–Roush procedure,[22] phosphonoacetamide **4** in dry THF was treated with 8-diazabicyclo[5.4.0]undec-7-ene in the presence of LiCl, followed by the addition of benzaldehyde at room temperature.[23] The reaction was completed within 2 h, and a >98:02 ratio[24] of *E*:*Z* α,β-unsaturated amide **11a** was obtained in 93% yield (Table 1, entry 1). Identical results were obtained in the reaction of **4** with *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and trimethylacetaldehyde (Table 1, entries 2–4). However, only moderate selectivity *E*:*Z* = 87:13 was obtained with isobutyraldehyde and isovaleraldehyde (Table 1, entries 5 and 6). These results suggest that the stereoselectivity in the HWE reaction of **4** with aromatic and alkyl aldehydes is determined by the steric hindrance at the α-position in the corresponding aldehydes.

Table 1. HWE reaction of **4** with several aldehydes



Entry		R	Yield[a] (%)	*E*:*Z*[b]
1	**a**	C_6H_5	93	98:02
2	**b**	*p*-Cl–C_6H_4	94	98:02
3	**c**	*p*-MeO–C_6H_4	97	98:02
4	**d**	*t*-Bu	92	98:02
5	**e**	*i*-Pr	94	83:17
6	**f**	*i*-Bu	95	83:17
7	**e**	*i*-Pr	92	96:04[c]
8	**f**	*i*-Bu	90	93:07[c]

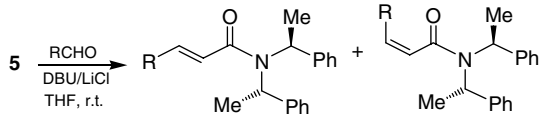
[a] Isolated yield after purification by column chromatography.
[b] The *E*:*Z* ratio was determined by ^{1}H NMR on crude product on the basis of the olefinic protons.
[c] The reaction was carried out in toluene at 100 °C.

On the other hand, it is generally accepted that the stereoselectivity in the HWE reactions is a result of both kinetic and thermodynamic control upon the reversible formation of the *erythro* and *threo* adducts and their decomposition to olefins.[7] Therefore, the stereochemistry is determined by a combination of the stereoselectivity in the initial carbon–carbon bond-forming step and reversibility of the intermediate adducts. The predominant formation of the *E*-olefins in the case of dialkylphosphono derivatives can be explained by the formation of thermodynamically more stable *threo* adducts. In this context, when we carried out the HWE reaction of **4** with isobutyraldehyde and isovaleraldehyde in toluene at 100 °C, a good *E*-selectivity and yield of α,β-unsaturated amides **11e**–**f** were obtained (Table 1, entries 7 and 8).[25]

In a similar way, the reaction of phosphonoacetamide **5** afforded the chiral α,β-unsaturated amides **12a**–**f** with excellent *E*-selectivity and yield. The results are summarized in Table 2.[26]

On the other hand, the HWE reaction of **6** with benzaldehyde, *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and trimethylacetaldehyde at room temperature provided the (*S*)-(*E*)-α,β-unsaturated amides **13a**–**d** as the only product (Table 3, entries 1–4).[27] However, the reaction of **6** with isobutyraldehyde and isovaleraldehyde under the same conditions, gave the α,β-unsaturated amides **13e**–**f** with low selectivities *E*:*Z* (Table 3, entries 5 and 6), whereas at

Table 2. HWE reaction of **5** with several aldehydes

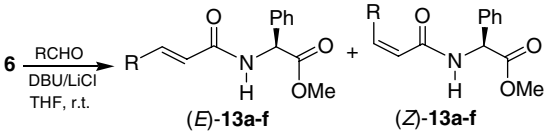


Entry		R	Yield[a] (%)	(*E*):(*Z*)[b]
1	**a**	C_6H_5	93	98:02
2	**b**	*p*-Cl–C_6H_4	94	98:02
3	**c**	*p*-MeO–C_6H_4	91	98:02
4	**d**	*t*-Bu	92	98:02
5	**e**	*i*-Pr	99	81:19
6	**f**	*i*-Bu	99	85:15
7	**e**	*i*-Pr	95	95:05[c]
8	**f**	*i*-Bu	93	95:05[c]

[a] Isolated yield after purification by column chromatography.
[b] The *E*:*Z* ratio was determined by ^{1}H NMR on the crude product.
[c] The reaction was carried out in toluene at 100 °C.

50 °C the chiral α,β-unsaturated amides **13e–f** were obtained with better *E*-selectivities (Table 3, entries 7 and 8).

Table 3. HWE reaction of **6** with several aldehydes



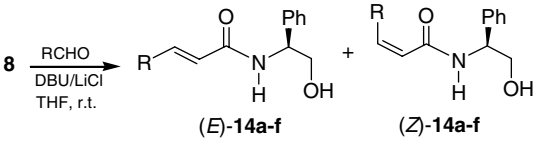
Entry		R	Yield[a] (%)	(*E*):(*Z*)[b]
1	**a**	C_6H_5	80	98:02
2	**b**	*p*-Cl–C_6H_4	90	98:02
3	**c**	*p*-MeO–C_6H_4	90	98:02
4	**d**	*t*-Bu	70	98:02
5	**e**	*i*-Pr	88	47:53
6	**f**	*i*-Bu	90	65:35
7	**e**	*i*-Pr	90	62:38[c]
8	**f**	*i*-Bu	91	83:17[c]

[a] Isolated yield after purification by column chromatography.
[b] The *E*:*Z* ratio was determined by ^{1}H NMR on the crude product.
[c] The reaction was carried out at 50 °C.

Finally, an excellent *E*-selectivity and good yield were obtained in the reaction of phosphonoacetamide **8** with benzaldehyde, *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde, trimethylacetaldehyde and isovaleraldehyde (Table 4, entries 1–5), where only the (*S*)-(*E*)-α,β-unsaturated amides **14a–e** were detected by ^{1}H NMR, whereas the reaction of **8** with isobutyraldehyde afforded the α,β-unsaturated amides **14f** with a selectivity *E*:*Z* = 90:10 and 89% (Table 4, entry 5). On the other hand, the reaction of **7** with isobutyraldehyde gave the α,β-unsaturated amides **14f** with a selectivity *E*:*Z* = 70:30 and 97% yield (Table 4, entry 7), whereas the reaction with isovaleraldehyde produced the chiral α,β-unsaturated amides **14e** with a selectivity *E*:*Z* = 94:06 and 88% yield (Table 4, entry 8). These results show that diethylphosphonoacetamide **8** gave an *E*-selectivity higher than dimethylphosphonoacetamide **7**.

No loss in the enantiomeric purity for phosphonoacetamides **6** and **8** was observed in the process by control experiment, in which **6** and **8** were submitted to the reaction conditions in the absence of the aldehyde at room temperature and 50 °C, recovering the corresponding phosphonoacetamides **6** and **8** without any loss in specific rotation.

Table 4. HWE reaction of **7** and **8** with several aldehydes



Entry		R	Yield[a] (%)	(*E*):(*Z*)[b]
1	**a**	C_6H_5	89	98:02
2	**b**	*p*-Cl–C_6H_4	84	98:02
3	**c**	*p*-MeO–C_6H_4	87	98:02
4	**d**	*t*-Bu	89	98:02
5	**e**	*i*-Bu	81	98:02
6	**f**	*i*-Pr	89	90:10
7	**f**	*i*-Pr	97	70:30[c]
8	**e**	*i*-Bu	88	94:06[c]

[a] Isolated yield after purification by column chromatography.
[b] The *E*:*Z* ratio was determined by ^{1}H NMR in the crude product.
[c] The reaction was carried out using the phosphonoacetamide **7**.

3. Conclusions

In conclusion, we have developed a practical and efficient methodology for the synthesis of chiral phosphonoacetamides **4–8**, and chiral α,β-unsaturated amides **11–14** in excellent *E*-selectivity under thermodynamic control. These chiral (*E*)-α,β-unsaturated amides should be excellent building blocks in organic synthesis.

4. Experimental

Optical rotations were taken on a Perkin–Elmer 241 polarimeter in a 1 dm tube; concentrations are given in g/100 mL. For the flash chromatography, Silica Gel 60 (230–400 mesh ASTM) was used. ^{1}H NMR spectra were registered on a Varian Mercury 200 and 300 MHz, INOVA 400 (400 MHz) and ^{13}C NMR on a Varian Mercury 50 and 75 MHz, and INOVA (100 MHz), and ^{31}P NMR on a Varian Mercury 200 (81 MHz). The spectra were recorded in $CDCl_3$, DMSO-d_6 and CD_3OD solution, using TMS as the internal reference. HRMS spectra were recorded on a JEOL JMS-700. Microanalyses were registered on an Elemental VARIO EL III. Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in desiccators over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.

4.1. Typical procedure for the preparation of chiral α-bromoacetamides

To a mixture of K_2CO_3 (0.77 g, 5.6 mmol) and (*S*)-(α-methylbenzyl)benzylamine (0.85 g, 4.0 mmol) in dichloro-

methane/water (3:2) (50 mL) at 0 °C, was added dropwise bromoacetyl bromide (0.81 g, 0.82 mL, 4.0 mmol). The reaction mixture was stirred overnight at 25 °C, quenched with water (30 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 9:1), obtaining (*S*)-2-bromoacetyl-(α-methylbenzyl)benzylamine **1** (1.29 g, 95%) as a viscous oil, $[\alpha]_D = -115.1$ (*c* 2.8, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ 1.41 (d, *J* = 7.2 Hz, 3H, CH_3(CH)Ph), 4.06–4.17 (m, 3H, CH_2Br and CH_2Ph), 4.55 (AB system, *J* = 16.7 Hz, 1H, CH_2Ph), 5.45 (br, 1H, CH(CH_3)Ph), 7.04–7.30 (m, 10H, H_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 18.6 (CH_3(CH)Ph), 46.8 (CH_2Ph), 54.4 (CH(CH_3)Ph), 61.5 (CH_2Br), 127.2, 127.6, 127.8(2), 128.7, 129.0, 139.1, 141.5, 173.0 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{17}H_{19}BrNO$, 332.0650; found, 332.0656. Anal. Calcd for $C_{17}H_{18}BrNO$: C, 61.46; H, 5.46; N, 4.22. Found: C, 61.62; H, 5.55; N, 4.33.

4.1.1. (*S*,*S*)-2-Bromoacetyl-bis(α-methylbenzyl)amine 2. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 7:3), obtaining (*S*,*S*)-**2** (97%) as a white solid, mp 93–94 °C, $[\alpha]_D = -127$ (*c* 3.52, $CHCl_3$); lit.[28] mp 94–95 °C, $[\alpha]_D = -125$ (*c* 3.52, $CHCl_3$).

4.1.2. (*S*)-Methyl 2-(2-bromoacetamide)-2-phenylacetate 3. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 50:50), obtaining (*S*)-**3** (91%) as a white solid, mp 72 °C, $[\alpha]_D = +120.79$ (*c* 1.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 3.75 (s, 3H, CO_2CH_3), 3.86 (AB system, *J* = 13.6 Hz, 1H, CH_2Br), 3.91 (AB system, *J* = 13.6 Hz, 1H, CH_2Br), 5.54 (d, *J* = 7.2 Hz, 1H, CHPh), 7.36–7.38 (m, 5H, H_{arom}), 7.48 (d, *J* = 7.2 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 28.9 (CH_2Br), 53.2 (CO_2CH_3), 57.1 (CHPh), 127.3, 128.9, 129.2, 135.8, 165.0 (CONH), 170.8 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{11}H_{13}BrNO_3$, 286.0079; found, 286.0069.

4.2. Typical procedure for the preparation of the α-(dimethoxyphosphoryl)acetamides

A mixture of **1** (1.3 g, 3.9 mmol) and trimethyl phosphite (1.45 g, 1.38 mL, 11.7 mmol) without solvent was heated for 5 h at 105–110 °C. The reaction mixture was cooled and the volatile materials were evaporated in a Kugel-rohr under a reduced pressure, after which the crude product was purified by flash column chromatography (EtOAc/Hex/MeOH, 5:3:2) to give (*S*)-2-(dimethoxyphosphoryl-acetyl)-(α-methylbenzyl)benzylamine **4** (1.38 g, 98%) as a viscous oil, $[\alpha]_D = -80.5$ (*c* 2.14, $CHCl_3$). ^{1}H NMR (72:28 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, $CDCl_3$, 25 °C): δ 1.47 (d, *J* = 7.2 Hz, 3H, CH_3CH), 1.53* (d, *J* = 6.8 Hz, 3H, CH_3CH), 2.94 (dd, $J_{H/P}$ = 31 Hz, J_{gem} = 14.8 Hz, 1H, CH_2P), 2.99* (dd, $J_{H/P}$ = 31, J_{gem} = 14.8 Hz, 1H, CH_2P), 3.22 (dd, $J_{H/P}$ = 23, J_{gem} = 14.8 Hz, 1H, CH_2P), 3.28* (dd, $J_{H/P}$ = 23, J_{gem} = 14.8 Hz, 1H, CH_2P), 3.78 (d, *J* = 11.2 Hz, 6H, $(CH_3O)_2P$), 3.83* (d, *J* = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.86* (d, *J* = 11.2 Hz, 3H, $(CH_3O)_2P$), 4.01* (AB system, *J* = 15.8 Hz, 1H, CH_2Ph), 4.31 (AB system, *J* = 18.4 Hz, 1H, CH_2Ph), 4.66 (AB system, *J* = 18.4 Hz, 1H, CH_2Ph), 4.97* (AB system, *J* = 15.8 Hz, 1H, CH_2Ph), 5.40* (q, *J* = 6.8 Hz, 1H, CH(CH_3)Ph), 6.15 (q, *J* = 7.2 Hz, 1H, CH(CH_3)Ph), 7.08–7.37 (m, 10H, H_{arom}), 7.08–7.37* (m, 10H, H_{arom}). ^{13}C NMR (72:28 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$, 25 °C): δ 17.3 (CH_3(CH)Ph), 19.5* (CH_3(CH)Ph), 33.4* (d, *J* = 132.8 Hz, CH_2P), 33.9 (d, *J* = 132.8 Hz, CH_2P), 46.7* (CH_2Ph), 47.9 (CH_2Ph), 52.5 (CH(CH_3)Ph), 53.3 (d, *J* = 5.7 Hz, $(CH_3O)_2P$), 53.4* (d, *J* = 6.9 Hz, $(CH_3O)_2P$), 53.5 (d, *J* = 6.9 Hz, $(CH_3O)_2P$), 53.6* (d, *J* = 6.9 Hz, $(CH_3O)_2P$), 57.3* (CH(CH_3)Ph), 125.9, 126.8*, 126.8, 127.2*, 127.4, 127.5, 127.6*, 127.9*, 128.4, 128.6*, 128.9, 137.8, 138.7*, 140.4*, 140.6, 165.7* (d, *J* = 6.1, (C=O)), 166.3 (d, *J* = 6.1, (C=O)). ^{31}P NMR (121 MHz, DMSO-d_6, 100 °C): δ 24.85. HRMS (FAB^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{19}H_{25}O_4NP$, 362.1521; found, 362.1510.

4.2.1. (*S*,*S*)-2-(Dimethoxyphosphorylacetyl)-bis(α-methylbenzyl)amine 5. The crude product was purified by flash column chromatography EtOAc/Hex/MeOH (5:4:1), to give (*S*,*S*)-**5** (95%) as viscous oil, $[\alpha]_D = -112.3$ (*c* 2.02, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C): δ 1.69 (d, *J* = 6.9 Hz, 3H, CH_3(CH)Ph), 3.08 (dd, $J_{H/P}$ = 21.3, J_{gem} = 9.0 Hz, 1H, CH_2P), 3.11 (dd, $J_{H/P}$ = 21.3, J_{gem} = 9.0 Hz, 1H, CH_2P), 3.64 (d, *J* = 10.9 Hz, 3H, $(CH_3O)_2P$), 3.65 (d, *J* = 10.9 Hz, 3H, $(CH_3O)_2P$), 5.05 (br, 1H, CH(CH_3)Ph), 7.09–7.14 (m, 10H, H_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C): δ 19.4 (CH_3(CH)Ph), 34.9 (d, *J* = 133.2 Hz, CH_2P), 53.2 (d, *J* = 6.2 Hz, $(CH_3O)_2P$), 53.3 (d, *J* = 6.2 Hz, $(CH_3O)_2P$), 54.9 (CH(CH_3)Ph), 127.3, 128.1, 128.3, 141.7, 165.0 (d, *J* = 5.1, (C=O)). ^{31}P NMR (121 MHz, DMSO-d_6, 100 °C): δ 25.86. HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{20}H_{27}NO_4P$, 376.1678; found, 376.1668.

4.2.2. (*S*)-Methyl 2-[2-(dimethoxyphosphoryl)acetamide]2-phenylacetate 6. The crude product was purified by flash column chromatography (EtOAc/Hex/MeOH, 5:3:2) to give the chiral phosphonoacetamide (*S*)-**6** (92%) as a white solid, mp 66–67 °C, $[\alpha]_D = +122.75$ (*c* 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (dd, $J_{H/P}$ = 19.0 Hz, J_{gem} = 15.6 Hz, 1H, CH_2P), 2.96 (dd, $J_{H/P}$ = 19.0, J_{gem} = 15.6 Hz, 1H, CH_2P), 3.71 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.72 (s, 3H, CO_2CH_3), 3.82 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 5.55 (d, *J* = 7.0 Hz, 1H, CHPh), 7.30–7.41 (m, 5H, H_{arom}), 7.74 (d, *J* = 7.0 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.4 (d, $J_{C/P}$ = 131.3 Hz, CH_2P), 53.0 (CO_2CH_3), 53.3 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 53.5 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 57.1 (CHPh), 127.4, 128.7, 129.1, 136.0, 163.3 (d, *J* = 3.8 Hz, CONH), 170.9 (CO_2CH_3). ^{31}P NMR (81 MHz, $CDCl_3$): δ 25.86. HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{13}H_{19}NO_6P$, 316.0950; found, 316.0943.

4.2.3. (*S*)-2-(2-Dimethoxyphosphoryl)acetamide-2-phenylethanol 7. To a solution of **6** (0.4 g, 1.27 mmol) in dry THF (20 mL) at 0 °C, sodium borohydride 290 mg, (7.62 mmol) was added. The resulting solution was heated

for 20 min at reflux, and then methanol (4 mL) was added dropwise and refluxed for an additional period of 60 min. After this time, the reaction mixture was cooled and an HCl/*i*-PrOH solution was added until pH 3–4. The solid was filtered and purified by column chromatography (EtOAc/Hex/*i*-PrOH, 5:3:3), to obtain the chiral phosphonoacetamide (*S*)-**7** (0.32 g, 89%) as a viscous oil, $[\alpha]_D = +34.5$ (*c* 2.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 2.93 (dd, $J_{H/P} = 16.8$, $J_{gem} = 14.8$ Hz, 1H, CH_2P), 2.87 (dd, $J_{H/P} = 16.8$, $J_{gem} = 14.8$ Hz, 1H, CH_2P), 3.65 (d, $J = 11.4$ Hz, 3H, $(CH_3O)_2P$), 3.73 (ddd, $J_{gem} = 11.6$, $J = 5.0$, $J = 1.2$ Hz, 1H, CH_2OH), 3.74 (d, $J = 11.4$ Hz, 3H, $(CH_3O)_2P$), 3.80 (ddd, $J_{gem} = 11.6$, $J = 7.6$, $J = 1.2$ Hz, 1H, CH_2OH), 5.04 (ddd, $J = 7.6$, $J = 5.0$ Hz, 1H, CHPh), 7.18–7.30 (m, 5H, H_{arom}), 7.65 (d, $J = 7.6$ Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.8 (d, $J = 130.5$ Hz, CH_2P), 53.3 (d, $J = 6.8$ Hz, $(CH_3O)_2P$), 53.7 (d, $J = 6.8$ Hz, $(CH_3O)_2P$), 66.0 (CH_2OH), 126.8, 127.7, 128.7, 139.0, 164.1 (d, $J =$ 4.6 Hz, CONH). ^{31}P NMR (81 MHz, $CDCl_3$): δ 26.77;. HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{12}H_{19}NO_5P$, 288.0995; found, 288.0979.

4.2.4. (*S*)-2-(2-Diethoxyphosphoryl)acetamide-2-phenylethanol 8. A solution of dicyclohexylcarbodiimide (DCC) (1.51 g, 7.3 mmol), 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (80 mg, 0.66 mmol) in 70 mL of dry dichloromethane was slowly added under an inert atmosphere at 0 °C to a solution of L-phenylglycinol (1.0 g, 7.3 mmol) and 2-(diethoxyphosphoryl)acetic acid **10** (1.57 g, 8.03 mmol) in 70 mL of dry dichloromethane. The reaction mixture was stirred for 12 h at room temperature, filtered and concentrated in vacuum. The crude product was purified by column chromatography (EtOAc/Hex/*i*-PrOH, 5:3:3) obtaining phosphonoacetamide (*S*)-**8** (2.14 g, 93% yield) as a viscous oil, $[\alpha]_D = +41.8$ (*c* 2.88, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, $J = 6.8$ Hz, 3H, $(CH_3CH_2O)_2P$), 1.31 (t, $J = 6.8$ Hz, 3H, $(CH_3CH_2O)_2P$), 2.91 (dd, $J_{H/P} = 18.4$, $J_{gem} = 14.4$ Hz, 1H, CH_2P), 2.96 (dd, $J_{H/P} = 18.4$, $J_{gem} = 14.4$ Hz, 1H, CH_2P), 3.77 (ddd, $J_{gem} = 10.8$, $J = 6.8$, $J = 1.2$ Hz, 1H, CH_2OH), 3.82 (ddd, $J_{gem} = 10.8$, $J = 4.4$, $J = 1.2$ Hz, 1H, CH_2OH), 4.05 (dq, $J_{H/P} = 14.0$, $J = 6.8$ Hz, 2H, CH_2OP), 4.14 (dq, $J_{H/P} = 14.0$, $J = 6.8$ Hz, 2H, CH_2O–P), 5.05–5.09 (m, 1H, CHPh), 7.23–7.35 (m, 5H, H_{arom}), 7.72 (br, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 ($(CH_3CH_2O)_2P$), 16.6 ($(CH_3CH_2O)_2P$), 35.0 (d, $J = 129.0$ Hz, CH_2P), 56.3 (CH_2OH), 63.0 (d, $J = 6.8$ Hz), (CH_2OP), 63.4 (d, $J = 6.8$ Hz, CH_2OP), 65.9 (CH_2Ph), 126.8, 127.6, 128.6, 139.1, 164.4 (CONH).^{31}P NMR (81 MHz, $CDCl_3$): δ 24.07. HMRS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{14}H_{23}NO_5P$, 316.1314; found, 316.1301.

4.3. General procedure for the HWE reaction

A solution of phosphonoacetamides **4**–**8** (1.0 equiv) in dry THF (30 mL) was treated under a nitrogen atmosphere with 8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.0 equiv) and lithium chloride (3.0 equiv) at room temperature. After stirring for 5 min, the corresponding aldehyde (1.0 equiv) was added and the reaction mixture stirred for 4 h at room temperature. The reaction was quenched by the addition of a saturated NH_4Cl solution, and extracted with ethyl acetate (3×40 mL). The combined extracts were washed with water (30 mL) followed by brine (30 mL), dried over Na_2SO_4 and concentrated in vacuum. The *E*:*Z* ratio was determined by ^1H NMR on the crude product, and then the (*S*)-(*E*)-α,β-unsaturated amides were purified by flash chromatography.

4.3.1. (*S*)-(*E*)-*N*-(Cinnamoyl)-(α-methylbenzyl)benzylamine 11a. (350 mg, 93%), as a viscous oil, $[\alpha]_D = -182.8$ (*c* 4.80, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 1.49 (d, $J = 6.6$ Hz, 3H, CH_3(CH)Ph), 4.36 (AB system, $J = 17.0$ Hz, 1H, CH_2Ph), 4.78 (AB system, $J = 17.0$ Hz, 1H, CH_2Ph), 5.81 (q, $J = 6.6$ Hz, 1H, $CH(CH_3)Ph$), 7.02 (d, $J_{trans} = 15.4$ Hz, 1H, CHC=O), 7.18–7.50 (m, $15H_{arom}$), 7.56 (d, $J_{trans} = 15.4$ Hz, 1H, CH–Ph). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 18.8 (CH_3(CH)Ph), 47.6 (CH_2Ph), 54.4 ($CH(CH_3)Ph$), 120.6, 127.2, 127.3, 127.7, 127.7, 128.3, 128.8, 128.9, 129.3 129.9, 135.9, 140.0, 141.9, 142.2, 167.2 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{24}H_{24}NO$, 342.1858; found, 342.1865.

4.3.2. (*S*)-(*E*)-*N*-(*p*-Chlorocinnamoyl)-(α-methylbenzyl)benzylamine 11b. (390 mg, 94%), as a viscous oil, $[\alpha]_D = -170.7$ (*c* 3.03 $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 1.49 (d, $J = 6.9$ Hz, 3H, CH_3(CH)Ph), 4.35 (AB system, $J = 16.9$ Hz, 1H, CH_2Ph), 4.78 (AB system, $J = 16.9$ Hz, 1H, CH_2Ph), 5.81 (q, $J = 6.9$ Hz, 1H, $CH(CH_3)Ph$), 7.10 (d, $J_{trans} = 15.1$ Hz, 1H, CHC=O), 7.14–7.56 (m, $14H_{arom}$) 7.54 (d, $J_{trans} = 15.1$ Hz, 1H, CH(*p*-ClC_6H_4)). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 18.6, (CH_3(CH)Ph), 47.6 (CH_2Ph), 54.6 ($CH(CH_3)Ph$), 121.2, 127.2, 127.3, 127.6, 127.8, 128.8, 129.0, 129.3, 129.8, 134.6, 134.8, 139.6, 140.7, 141.8, 167.3 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{24}H_{23}ClNO$, 376.1468; found, 376.1466.

4.3.3. (*S*)-(*E*)-*N*-(*p*-Methoxycinnamoyl)-(α-methylbenzyl)-benzylamine 11c. (400 mg, 97%), as a viscous oil, $[\alpha]_D = -185.3$ (*c* 2.42, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6, 120 °C): δ 1.51 (d, $J = 6.6$ Hz, 3H, CH_3(CH)Ph), 3.78 (s, 3H, CH_3O), 4.37 (AB system, $J = 16.8$ Hz, CH_2Ph), 4.78 (AB system, $J = 16.8$ Hz, CH_2Ph), 5.82 (q, $J = 6.6$ Hz, 1H, $CH(CH_3)Ph$), 6.91 (AA′BB′ system, $J = 8.8$ Hz, 2H, H_{arom}), 7.20 (d, $J_{trans} = 15.2$ Hz, 1H, CHC=O), 7.17–7.46 (m, 12H, H_{arom}), 7.54 (d, $J_{trans} = 15.2$ Hz 1H, CHAr). ^{13}C NMR (100 MHz, DMSO-d_6, 120 °C): δ 17.4 (CH_3(CH)Ph), 46.3 (CH_2Ph), 54.8 ($CH(CH_3)Ph$), 54.8 (CH_3O), 113.8, 116.8, 125.8, 126.0, 126.3, 126.4, 127.4, 127.6, 128.6, 138.9, 140.5, 140.6, 141.0, 160.0, 166.1 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{25}H_{26}NO_2$, 372.1964; found, 372.1956.

4.3.4. (*S*)-(*E*)-*N*-(3-*tert*-Butylacryloyl)-(α-methylbenzyl)benzylamine 11d. (330 mg, 92%), as a white solid, mp 63–64 °C, $[\alpha]_D = -156.3$ (*c* 2.63, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 0.92 (s, 9H, $(CH_3)_3C$), 1.46 (d, $J = 6.9$ Hz, 3H, CH_3(CH)Ph), 4.31 (AB system, $J = 16.8$ Hz, 1H, CH_2Ph), 4.64 (AB system, $J = 16.8$ Hz, 1H, CH_2Ph), 5.69 (br, 1H, $CH(CH_3)Ph$), 6.08 (d, J_{trans}= 15.3 Hz, 1H, CHC=O), 6.68 (d, $J_{trans} = 15.3$ Hz, 1H,

$CH(CH_3)_3$), 7.10–7.33 (m, 10H, H_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 18.6(CH_3(CH)Ph), 29.4 (($CH_3)_3C$), 33.8 ($C(CH_3)_3$), 47.8 (CH_2Ph), 54.2 ($CH(CH_3)Ph$), 118.6, 127.2, 127.3, 127.6, 127.7, 128.7, 128.9, 139.9, 142.2, 155.3, 167.8 (C=O). HRMS (Cl^+, CH_4) m/z: (MH^+) calcd for $C_{22}H_{28}NO$, 322.2171; found, 322.2166.

4.3.5. (*S*)-(*E*)-*N*-(3-*iso*-Propylacryloyl)-(α-methylbenzyl)-benzylamine 11e. (320 mg, 94%), as a viscous oil. ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 0.91 (d, $J = 6.8$ Hz, 3H, $(CH_3)_2CH$), 0.92 (d, $J = 6.8$ Hz, 3H, $(CH_3)_2CH$), 1.45 (d, $J = 7.2$ Hz, 3H, CH_3(CH)Ph), 2.31–2.38 (m, 1H, $CH(CH_3)_2$), 4.28 (AB system, $J = 16.8$ Hz, 1H, CH_2Ph), 4.65 (AB system, $J = 16.8$ Hz, 1H, CH_2Ph), 5.69 (br, 1H, $CH(CH_3)Ph$), 6.19 (d, $J_{trans} = 15.1$ Hz, 1H, CHC=O), 6.70 (dd, $J_{trans} = 15.1$ Hz, $J = 6.8$ Hz, 1H, CH*i*-Pr), 7.15–7.34 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C): δ 18.7 (CH_3(CH)Ph), 22.1 (($CH_3)_2CH$), 30.9, ($CH(CH_3)_2$), 47.6 (CH_2Ph), 54.2 ($CH(CH_3)Ph$), 120.3, 127.1, 127.3, 127.6, 128.7, 128.9, 128.9, 140.0, 142.3, 151.8, 167.4 (C=O). HRMS (Cl^+, CH_4) m/z: (MH^+) calcd for $C_{21}H_{26}NO$, 308.2014; found, 308.2009.

4.3.6. (*S*)-(*E*)-*N*-(3-*iso*-Butylacryloyl)-(α-methylbenzyl)benzylamine 11f. (340 mg, 95%), as a viscous oil, $[\alpha]_D = -142.8$ (*c* 2.0, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 0.81 (d, $J = 6.6$ Hz, 3H, $(CH_3)_2CH$), 0.82 (d, $J = 6.6$ Hz, 3H, $(CH_3)_2CH$), 1.44 (d, $J = 7.2$ Hz, 3H, CH_3(CH)Ph), 1.64 (n, $J = 6.6$ Hz, 1H, $CH(CH_3)_2$), 2.01 (t, $J = 6.6$ Hz, 2H, $CH_2CH(CH_3)_2$), 4.26 (AB system, $J = 17.1$ Hz, 1H, CH_2Ph), 4.65 (AB system, $J = 17.1$ Hz, 1H, CH_2Ph), 5.69 (br, 1H, $CH(CH_3)Ph$), 6.27 (d, $J_{trans} = 14.7$ Hz, 1H, CHC=O), 6.72 (dt, $J_{trans} = 15.0$ Hz, $J = 7.2$ Hz, 1H, $CHCH_2i$-Pr), 7.10–7.34 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C): δ 18.7 (CH_3(CH)Ph), 22.7 (($CH_3)_2CH$), 22.8 (($CH_3)_2CH$), 28.1 ($CH_2CH(CH_3)_2$), 41.6 ($CH(CH_3)_2$), 47.4 (CH_2Ph), 54.1 ($CH(CH_3)Ph$), 123.9, 127.1, 127.2, 127.6, 127.7, 128.7, 128.9, 140.0, 142.2, 144.3, 167.2 (C=O). HRMS (Cl^+, CH_4) m/z: (MH^+) calcd for $C_{22}H_{28}NO$, 322.2171; found, 322.2163.

4.3.7. (*S*,*S*)-(*E*)-*N*-(Cinnamoyl)-bis(α-methylbenzyl)amine 12a. (352 mg, 93%), as a white solid, mp 151–152 °C, $[\alpha]_D = +6.8$ (*c* 3.22, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6, 110 °C): δ 1.75 (d, $J = 7.2$ Hz, 6H, CH_3(CH)Ph), 5.38 (br, 2H, $CH(CH_3)Ph$), 6.71 (d, $J_{trans} = 15.8$ Hz, 1H, CHC=O), 7.16–7.36 (m, 15H, H_{arom}), 7.40 (d, $J_{trans} = 15.8$ Hz, 1H, CHPh). ^{13}C NMR (100 MHz, DMSO-d_6, 110 °C): δ 18.9 (CH_3(CH)Ph), 52.5 ($CH(CH_3)Ph$), 121.5, 126.5, 127.0, 127.1, 127.6, 128.4, 128.9, 135.1, 139.6, 141.4, 165.4 C=O. HRMS (FAB^+, CH_4) m/z: (MH^+) calcd for $C_{25}H_{26}NO$, 356.2014; found, 356.2010. Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.05; H, 7.14; N, 4.14.

4.3.8. (*S*,*S*)-(*E*)-*N*-(*p*-Chlorocinnamoyl)-bis(α-methylbenzyl)amine 12b. (390 mg, 94%), as a white solid, mp 123–124 °C, $[\alpha]_D = +48.3$ (*c* 3.66, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 1.69 (d, $J = 6.9$ Hz, 6H, CH_3(CH)Ph), 5.31 (br, 2H, $CH(CH_3)Ph$), 6.61 (d, $J_{trans} = 15.4$ Hz, 1H, CHC=O), 7.08–7.30 (m, 14H, H_{arom}), 7.28 (d, $J_{trans} = 15.4$ Hz, 1H, CH(*p*-ClC_6H_4)). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 19.7 (CH_3(CH)Ph), 53.5 ($CH(CH_3)Ph$), 123.1, 127.6, 127.8, 128.6, 129.3, 129.6, 134.6, 134.7, 139.2, 142.0, 166.4 C=O. HRMS (FAB^+, CH_4) m/z: (MH^+) calcd for $C_{25}H_{25}ClNO$, 390.1625; found, 390.1638. Anal. Calcd for $C_{25}H_{24}ClNO$: C, 77.01; H, 6.20; N, 3.59. Found: C, 76.98; H, 6.29; N, 3.69.

4.3.9. (*S*,*S*)-(*E*)-*N*-(*p*-Methoxycinnamoyl)-bis(α-methylbenzyl)amine 12c. (374 mg, 91%), as a white solid, mp 102–103 °C, $[\alpha]_D = +56.4$ (*c* 3.77, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6, 120 °C): δ 1.75 (d, $J = 7.2$ Hz, 6H, CH_3(CH)Ph), 3.77 (s, 3H, CH_3O), 5.37 (q, $J = 7.2$ Hz, 2H, $CH(CH_3)Ph$), 6.57 (d, $J_{trans} = 15.2$ Hz, 1H, CHC=O), 6.88 (AA′BB′ system, $J = 8.4$ Hz, 2H, H_{arom}), 7.14–7.21 (m, 10H, H_{arom}), 6.30 (AA′BB′ system, $J = 8.4$ Hz, 2H, H_{arom}), 7.38 (d, $J_{trans} = 15.2$ Hz, 1H, CH(*p*-$MeOC_6H_4$)). ^{13}C NMR (100 MHz, DMSO-d_6, 120 °C): δ 19.1 (CH_3(CH)Ph), 52.7 ($CH(CH_3)Ph$), 55.4 (CH_3O), 114.4, 119.4, 126.6, 127.1, 127.8, 128.0, 128.9, 139.6, 141.7, 160.4, 165.9 C=O. HRMS (FAB^+, CH_4) m/z: (MH^+) calcd for $C_{26}H_{28}NO_2$, 386.2120; found, 386.2137. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.08; H, 7.18; N, 3.75.

4.3.10. (*S*,*S*)-(*E*)-*N*-(3-*tert*-Butylacryloyl)-bis(α-methylbenzyl)amine 12d. (330 mg, 92%), as a white solid, mp 114 °C, $[\alpha]_D = -170.9$ (*c* 3.64, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 0.79 (s, (($CH_3)_3C$)), 1.65 (d, $J = 7.2$ Hz, 6H, CH_3(CH)Ph), 5.31 (br, 2H, $CH(CH_3)Ph$), 5.67 (d, $J_{trans} = 15.4$ Hz, 1H, CH=CO), 6.49 (d, $J_{trans} = 15.4$ Hz, 1H, $CHC(CH_3)_3$), 7.08–7.19 (m, 10H, H_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 19.7 (CH_3(CH)Ph), 29.3 (($CH_3)_3C$), 33.6 ($C(CH_3)_3$), 52.8 ($CH(CH_3)Ph$), 120.4, 127.5, 127.7, 128.6, 142.2, 154.0, 167.2 C=O. HRMS (FAB^+, CH_4) m/z: (MH^+) calcd for $C_{23}H_{30}ON$, 336.2327; found, 336.2332. Anal. Calcd for $C_{23}H_{29}ON$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.54; H, 8.81; N, 4.22.

4.3.11. (*S*,*S*)-(*E*)-*N*-(3-*iso*-Propylacryloyl)-bis(α-methylbenzyl)amine 12e. (340 mg, 99%), as a viscous oil. ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 0.82 (d, $J = 6.7$ Hz, 3H, $(CH_3)_2CH$), 0.84 (d, $J = 6.7$ Hz, 3H, $(CH_3)_2CH$), 1.68 (d, $J = 7.2$ Hz, 6H, CH_3(CH)Ph), 2.20–2.27 (m, 1H, $CH(CH_3)_2$), 5.30 (q, $J = 7.2$ Hz, 2H, $CH(CH_3)Ph$), 5.87 (dd, $J_{trans} = 15$, $J_{allylic} = 1.2$ Hz, 1H, CHC=O), 6.55 (dd, $J_{trans} = 15$, $J = 6.7$ Hz, 1H, CH*i*-Pr), 7.10–7.20 (m, 10H, H_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 19.7 (CH_3(CH)Ph), 21.9 (($CH_3)_2CH$), 22.0 (($CH_3)_2CH$), 30.7 ($CH(CH_3)_2$), 53.0 ($CH(CH_3)Ph$), 122.2, 127.3, 127.8, 128.5, 142.4, 150.2, 166.7 C=O. HRMS (CI^+, CH_4) m/z: (MH^+) calcd for $C_{22}H_{28}ON$, 322.2171; found, 322.2169.

4.3.12. (*S*,*S*)-(*E*)-*N*-(3-*iso*-Butylacryloyl)-bis(α-methylbenzyl)amine 12f. (360 mg, 99%), as a white solid, mp 64–65 °C, $[\alpha]_D = -81.7$ (*c* 1.66, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6, 100 °C): δ 0.78 (d, $J = 6.7$ Hz, 3H, $(CH_3)_2CH$), 0.79 (d, $J = 6.7$ Hz, 3H, $(CH_3)_2CH$), 1.59 (m, 1H, $CH(CH_3)_2$), 1.69 (d, $J = 6.9$ Hz, 6H, CH_3(CH)Ph), 1.90

(m, 2H, CH_2*i*-Pr), 5.27 (q, $J = 6.9$ Hz, 2H, $CH(CH_3)Ph$), 6.00 (dt, $J_{trans} = 15$, $J_{allylic} = 1.5$ Hz, 1H, CHC=O), 6.57 (dt, $J_{trans} = 15$, $J = 7.2$ Hz, 1H, CH*i*-Bu), 7.09–7.20 (m, 10H, H_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ 19.8 ($CH_3(CH)Ph$), 22.7 ($(CH_3)_2CH$), 22.8 ($(CH_3)_2CH$), 28.0 (CH_2*i*-Pr), 41.6 ($CH(CH_3)_2$), 53.2 ($(CH(CH_3)Ph)$), 125.9, 127.3, 127.8, 128.5, 142.3, 142.7, 166.4 C=O. HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{23}H_{30}ON$, 336.2327; found, 336.2342.

4.3.13. (*S*)-(*E*)-Methyl *N*-(cinnamoyl)-2-amino-2-phenylacetate 13a. (150 mg, 82%), as a white solid, mp 158 °C, $[\alpha]_D = +39.9$ (*c* 1.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H, CO_2CH_3), 5.74 (d, $J = 6.8$ Hz, 1H, CHPh), 6.49 (d, $J_{trans} = 15.4$ Hz, 1H, CHCO), 6.78 (d, $J = 6.8$ Hz, 1H, NH), 7.33–7.49 (m, 10H, H_{arom}), 7.63 (d, $J_{trans} = 15.4$ Hz, 1H, CHPh). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.1 (CO_2CH_3), 56.7 (CHPh), 119.9, 127.5, 128.1, 128.8, 128.9, 129.2, 130.1, 134.8, 136.7, 142.3, 165.3 (CONH), 171.7 (CO_2Me). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{18}H_{18}NO_3$, 296.1281; found, 296.1287. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.17; H, 5.86; N, 4.81.

4.3.14. (*S*)-(*E*)-Methyl *N*-(*p*-chlorocinnamoyl)-2-amino-2-phenylacetate 13b. (289 mg, 93%), as a white solid, mp 183 °C, $[\alpha]_D = +69.8$ (*c* 1.1 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H, CO_2CH_3), 5.71 (d, $J = 7.0$ Hz, 1H, CHPh), 6.46 (d, $J_{trans} = 15.8$ Hz, 1H, CHCO), 6.87 (d, $J = 7.0$ Hz, 1H, NH), 7.29–7.40 (m, 9H, H_{arom}), 7.56 (d, $J_{trans} = 15.8$ Hz, 1H, CHAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.1 (CO_2CH_3), 56.7 (CHPh), 120.5, 127.5, 128.8, 129.1, 129.2, 129.2, 133.2, 135.8, 136.5, 140.9, 165.0 (CONH), 171.7 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{18}H_{17}ClNO_3$, 330.0891; found, 330.0892. Anal. Calcd for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.26; H, 4.94; N, 4.23.

4.3.15. (*S*)-(*E*)-Methyl *N*-(*p*-methoxycinnamoyl)-2-amino-2-phenylacetate 13c. (271 mg, 86%), as a white solid, mp 146–147 °C, $[\alpha]_D = -2.2$ (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CH_3OAr), 5.73 (d, $J = 7.0$ Hz, 1H, CHPh), 6.36 (d, $J_{trans} = 15.6$ Hz, 1H, CHCO), 6.74 (d, $J = 7.0$ Hz, 1H, NH), 6.86 (AA′BB′ system, $J = 8.8$ Hz, 2H, H_{arom}), 7.33–7.44 (m, 7H, H_{arom}), 7.59 (d, $J_{trans} = 15.6$ Hz, 1H, CHAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0 (CO_2CH_3), 56.7 (CHPh), 114.4, 117.5, 127.4, 127.5, 128.7, 129.1, 129.6, 136.8, 141.8, 161.2, 165.7 (CONH), 171.8 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{19}H_{20}NO_4$, 326.1387; found, 326.1379. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.98; H, 5.90; N, 4.38.

4.3.16. (*S*)-(*E*)-Methyl *N*-(3-*tert*-butylacryloyl)-2-amino-2-phenylacetate 13d. (184 mg, 70%), as a white solid, mp 133–134 °C, $[\alpha]_D = -1.1$ (*c* 2.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H, $(CH_3)_3C$), 3.74 (s, 3H, CO_2CH_3), 5.68 (d, $J = 7.0$ Hz, 1H, CHPh), 5.75 (d, $J_{trans} = 15.4$ Hz, 1H, CHCO), 6.56 (d, $J = 7.0$ Hz, 1H, NH), 6.88 (d, $J_{trans} = 15.4$ Hz, 1H, CH*t*-Bu), 7.31–7.40, (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9 ($(CH_3)_3CH$), 33.7 ($CH(CH_3)_3$), 53.0 (CO_2CH_3), 56.5 (CHPh), 118.1, 127.4, 128.6, 129.0, 136.6, 156.0, 165.6 (CONH), 171.6 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: calcd for (MH^+) $C_{16}H_{22}NO_3$, 276.1600; found, 276.1606. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.79; H, 7.76; N, 5.19.

4.3.17. (*S*)-(*E*)-13e and (*S*)-(*Z*)-Methyl *N*-(3-*iso*-propylacryloyl)-2-amino-2-phenylacetate 13e.

4.3.17.1. (*S*)-(*E*)-Isomer 13e (more polar). (143 mg, 56%), as a white solid, mp 98–100 °C, $[\alpha]_D = +0.7$ (*c* 2.37, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, $J = 7.0$ Hz, 6H, $(CH_3)_2CH$), 2.42 (m, 1H, $CH(CH_3)_2$), 3.73 (s, 3H, CO_2CH_3), 5.67 (d, $J = 7.2$ Hz, 1H, CHPh), 5.80 (dd, $J_{trans} = 15.4$, $J_{allylic} = 1.5$ Hz, 1H, CHCO), 6.59 (d, $J = 7.2$ Hz, 1H, NH), 6.85 (dd, $J_{trans} = 15.4$, $J = 7.0$ Hz, 1H, CH*i*-Pr), 7.31–7.39 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 ($(CH_3)_2CH$), 21.6 ($(CH_3)_2CH$), 30.9 ($CH(CH_3)_2$), 53.0 (CHPh), 56.5 (CO_2CH_3), 120.1, 127.4, 128.5, 129.0, 136.6, 152.3, 165.4 (CONH), 171.5 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{15}H_{21}NO_3$, 262.1438; found, 262.1461. Anal. Calcd for $C_{15}H_{20}NO_3$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.80; H, 7.27; N, 5.43.

4.3.17.2. (*S*)-(*Z*)-Isomer 13e (less polar). (88 mg, 34%), as a white solid, mp 125–126 °C, $[\alpha]_D = +7.2$ (*c* 1.36, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, $J = 6.8$ Hz, 3H, $(CH_3)_2CH$), 0.99 (d, $J = 6.8$ Hz, 3H, $(CH_3)_2CH$), 3.57–3.69 (m, 1H, $CH(CH_3)_2$), 3.73 (s, 3H, CO_2CH_3), 5.61 (d, $J = 5.6$ Hz, 1H, CHPh), 5.63 (dd, $J_{cis} = 10.4$, $J_{allylic} = 0.8$ Hz, 1H, CHCO), 5.85 (dd, $J_{cis} = 10.4$, $J = 11.6$ Hz, 1H, CH*i*-Pr), 6.50 (d, $J = 5.6$ Hz, 1H, NH), 7.31–7.39 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7 ($(CH_3)_2CH$), 22.8 ($(CH_3)_2CH$), 27.6 ($CH(CH_3)_2$), 53.0 (CHPh), 56.4 (CO_2CH_3), 119.0, 127.4, 128.6, 129.0, 136.7, 154.1, 165.4 (CONH), 171.5 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{15}H_{21}NO_3$, 262.1438; found, 262.1453. Anal. Calcd for $C_{15}H_{20}NO_3$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.78; H, 7.31; N, 5.41.

4.3.18. (*S*)-(*E*)-13f and (*S*)-(*Z*)-Methyl *N*-(3-*iso*-butylacryloyl)-2-amino-2-phenylacetate 13f.

4.3.18.1. (*S*)-(*E*)-Isomer 13f (more polar). (203 mg, 75%), as a white solid, mp 100 °C, $[\alpha]_D = +86.15$ (*c* 0.78, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, $J = 7.0$ Hz, 3H, $(CH_3)_2CH$), 0.91 (d, $J = 7.0$ Hz, 3H, $(CH_3)_2CH$), 1.73 (m, 1H, $CH(CH_3)_2$), 2.05 (dt, $J = 7.0$, 1.0 Hz, 2H, CH_2*i*-Pr), 3.73 (s, 3H, CO_2CH_3), 5.66 (d, $J = 7.2$ Hz, 1H, CHPh), 5.84 (dt, $J_{trans} = 15.1$, $J_{allylic} = 1.2$ Hz, 1H, CHC=O), 6.55 (d, $J = 7.2$ Hz, 1H, NH), 6.85 (dt, $J_{trans} = 15.1$, $J = 7.0$ Hz, 1H, CH*i*-Bu), 7.30–7.39 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6 ($(CH_3)_2CH$), 22.6 ($(CH_3)_2CH$), 28.0 ($CH(CH_3)_2$), 41.6 (CH_2*i*-Pr), 53.0 (CHPh), 56.5 (CO_2CH_3), 123.8, 127.4, 128.6, 129.0, 136.6, 145.1, 165.1 (CONH), 171.5 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{16}H_{22}NO_3$, 276.1594; found, 276.1609. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.31; H, 7.65; N, 5.15.

4.3.18.2. (*S*)-(*Z*)-Isomer 13f (less polar). (41 mg, 16%), as a white solid, mp 114–116 °C, $[\alpha]_D = +0.1$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, $J = 6.6$ Hz, 3H, $(CH_3)_2CH$), 0.91 (d, $J = 6.6$ Hz, 3H, $(CH_3)_2CH$), 1.69 (m, 1H, $CH(CH_3)_2$), 2.51 (m, 1H, CH_2*i*-Pr), 2.58 (m, 1H, CH_2*i*-Pr), 3.73 (s, 3H, CO_2CH_3), 5.62 (d, $J = 7.2$ Hz, 1H, CHPh), 5.79 (dt, $J_{cis} = 11.6$, $J_{allylic} = 1.8$ Hz, 1H, CHCO), 6.07 (dt, $J_{cis} = 11.6$, $J = 7.2$ Hz, 1H, CH*i*-Bu), 6.46 (d, $J = 7.2$ Hz, 1H, NH), 7.30–7.39 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5 ($(CH_3)_2CH$), 22.6 ($(CH_3)_2CH$), 28.8 ($CH(CH_3)_2$), 37.7 (CH_2*i*-Pr), 53.0 (CHPh), 56.4 (CO_2CH_3), 121.9, 127.4, 128.6, 129.1, 136.7, 146.4, 165.6 (CONH), 171.5 (CO_2CH_3). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{16}H_{22}NO_3$, 276.1594; found, 276.1592. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.57; H, 7.62; N, 5.13.

4.3.19. (*S*)-*N*-(Cinnamoyl)-2-amino-2-phenylethanol 14a.[29] (302 mg, 89%), as a white solid, mp 197 °C, $[\alpha]_D = -29.8$ (*c* 2.47, MeOH). ^1H NMR (400 MHz, CD_3OD): δ 3.77 (dd, $J_{gem} = 11.4$, $J = 8.0$ Hz, 1H, CH_2OH), 3.80 (dd, $J_{gem} = 11.4$, $J = 5.4$ Hz, 1H, CH_2OH), 5.12 (dd, $J = 7.2$, $J = 5.4$ Hz, 1H, CHPh), 6.76 (d, $J_{trans} = 15.8$ Hz, 1H, CHCO), 7.24–7.41 (m, 8H, H_{arom}), 7.54 (d, $J_{trans} = 15.8$ Hz, 1H, CH=C**H**Ph), 7.55–7.57 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 57.4 (CH_2OH), 66.3 (CHPh), 121.8, 128.0, 128.4, 128.8, 129.5, 129.9, 130.8, 136.3, 141.2, 142.0, 168.3 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{17}H_{18}NO_2$, 268.1338; found, 268.1333. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.04; H, 6.50; N, 5.33.

4.3.20. (*S*)-*N*-(*p*-Chlorocinnamoyl)-2-amino-2-phenylethanol 14b.[30] (290 mg, 84%), as a white solid, mp 164 °C, $[\alpha]_D = -51.1$ (*c* 2.1, MeOH). ^1H NMR (400 MHz, CD_3OD): δ 3.78 (dd, $J_{gem} = 10.8$, $J = 7.6$ Hz, CH_2OH), 3.82 (dd, $J_{gem} = 10.8$, $J = 5.2$ Hz 1H, CH_2OH), 5.11 (dd, $J = 7.6$, $J = 5.2$ Hz, 1H, CHPh), 6.73 (d, $J_{trans} = 15.6$ Hz, 1H, CHCO), 7.23–7.39 (m, 7H, H_{arom}), 7.54–7.49 (d, $J_{trans} = 15.6$ Hz, 1H, CHAr), 7.52 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 57.4 (CH_2OH), 66.3 (CHPh), 122.7, 128.0, 128.5, 129.5, 130.1, 130.3, 135.0, 136.5, 140.5, 141.1, 168.0 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{17}H_{17}ClNO_2$, 302.0948; found, 302.0946 Anal. Calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.51; H, 5.43; N, 4.70.

4.3.21. (*S*)-*N*-(*p*-Methoxycinnamoyl)-2-amino-2-phenylethanol 14c. (328 mg, 87%), as a white solid, mp 158 °C, $[\alpha]_D = -71.4$ (*c* 2.6, MeOH). ^1H NMR (400 MHz, CD_3OD): δ 3.76 (dd, $J_{gem} = 11.2$, $J = 7.6$ Hz, 1H, CH_2OH), 3.80 (s, 3H, CH_3OPh), 3.81 (dd, $J_{gem} = 11.2$, $J = 5.6$ Hz, 1H, CH_2OH), 5.11 (dd, $J = 7.6$, $J = 5.6$ Hz, 1H, CHPh), 6.61 (d, $J_{trans} = 15.8$ Hz, 1H, CHCO), 6.93 (AA′BB′ system, $J = 8.8$ Hz, 2H, H_{arom}), 7.23–7.38 (m, 5H, H_{arom}), 7.49 (d, $J_{trans} = 15.8$ Hz, 1H, CHAr), 7.50 (AA′BB′ system, $J = 8.8$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 55.9 (CH_2OH), 57.3 ($CH_3OC_6H_4$), 66.3 (CHPh), 115.4, 119.3, 128.1, 128.5, 128.9, 129.6, 130.6, 141.4, 141.9, 162.7, 168.9 (C=O). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.85; H, 6.44; N, 4.71.

4.3.22. (*S*)-(*E*)-*N*-(3-*tert*-Butylacryloyl)-2-amino-2-phenylethanol 14d. (275 mg, 88%), as a white solid, mp 177 °C, $[\alpha]_D = +97.5$ (*c* 2.74, MeOH). ^1H NMR (400 MHz, CD_3OD): δ 1.08 (s, 9H, $(CH_3)_3C$), 3.72 (dd, $J_{gem} = 11.6$, $J = 7.2$ Hz, 1H, CH_2OH), 3.77 (dd, $J_{gem} = 11.6$, $J = 5.6$ Hz, 1H, CH_2OH), 5.05 (dd, $J = 7.2$, $J = 5.6$ Hz, 1H, CHPh), 5.99 (d, $J_{trans} = 15.6$ Hz, 1H, CHC=O), 6.80 (d, $J_{trans} = 15.6$ Hz, 1H, CH*t*-Bu), 7.24–7.34, (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 29.3 ($(CH_3)_3CH$), 34.3 ($CH(CH_3)_3$), 57.2 (CH_2OH), 66.3 (CHPh), 120.2, 128.1, 128.5, 129.6, 141.4, 155.9, 168.9 (C=O). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.82; H, 8.71; N, 5.87.

4.3.23. (*S*)-(*E*)-*N*-(3-*iso*-Butylacryloyl)-2-amino-2-phenylethanol 14e. (254 mg, 81%), as a white solid, mp 117 °C, $[\alpha]_D = +66.2$ (*c* 0.95, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, $J = 6.8$ Hz, 6H, $(CH_3)_2CH$), 1.72 (m, 1H, $CH(CH_3)_2$), 2.03 (ddd, $J = 6.8$, $J_{allylic} = 1.2$ Hz, 2H, CH_2*i*-Pr), 3.54 (br, 1H, OH), 3.82 (s, 2H, CH_2OH), 5.05 (dd, $J = 12.0$, $J = 5.2$ Hz, 1H, CHPh), 5.84 (dd, $J_{trans} = 15.0$, $J_{allylic} = 1.2$ Hz, 1H, CHC=O), 6.59 (br, 1H, NH), 6.82 (dt, $J_{trans} = 15.0$, $J = 7.0$ Hz, 1H, CH*i*-Bu), 7.25–7.35 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7 ($(CH_3)_2CH$), 22.7 ($(CH_3)_2CH$), 28.1 ($CH(CH_3)_2$), 41.6 (CH_2*i*-Pr), 56.2 (CH_2OH), 66.5 (CHPh), 124.2, 126.8, 127.9, 128.9, 139.1, 144.9, 166.6 (C=O). HRMS (FAB^+) *m*/*z*: (MH^+) calcd for $C_{15}H_{22}NO_2$, 248.1651; found, 248.1664. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.51; H, 8.56; N, 5.78.

4.3.24. (*S*)-(*E*)-*N*-(3-*iso*-Propylacryloyl)-2-amino-2-phenylethanol 14f. (241 mg, 89%), as a white solid, mp 123–124 °C, $[\alpha]_D = +75.8$ (*c* 2.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, $J = 6.8$ Hz, 6H, $(CH_3)_2CH$), 2.42 (m, 1H, $CH(CH_3)_2$), 3.51 (br, 1H, OH), 3.83 (s, 2H, CH_2OH), 5.08 (dd, $J = 12.4$, $J = 5.2$ Hz, 1H, CHPh), 5.78 (dd, $J_{trans} = 15.6$, $J_{allylic} = 1.2$ Hz, 1H, CHC=O), 6.58 (d, $J = 6.8$ Hz, 1H, NH), 6.83 (dd, $J_{trans} = 15.6$, $J = 6.6$ Hz, 1H, CH*i*-Pr), 7.25-7.35 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 ($(CH_3)_2CH$), 21.7 ($(CH_3)_2CH$), 31.0 ($CH(CH_3)_2$), 56.2 (CH_2OH), 66.6 (CHPh), 120.5, 126.8, 127.9, 128.9, 139.1, 152.1, 166.9 (C=O). HRMS (CI^+, CH_4) *m*/*z*: (MH^+) calcd for $C_{14}H_{20}NO_2$, 234.1494; found, 234.1504. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.82; H, 8.21; N, 6.07.

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