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Highly Efficient Synthesis of Heterocyclic and Alicyclic β²-Amino Acid Derivatives by Catalytic Asymmetric Hydrogenation

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Abstract: A valuable class of new heterocyclic and alicyclic prochiral α-aminomethylacrylates has been conveniently synthesized through a three-step transformation involving a Baylis–Hillman reaction, *O*-acetylation, and a subsequent allylic amination. The corresponding novel β²-amino acid derivatives were prepared with excellent enantioselectivities and high yields by catalytic asymmetric hydrogenation using the catalyst rhodium(Et-Duphos) (Et-Duphos = 2′,5′,2″,5″-tetraethyl-1,2-bis(phospholanyl)benzene)) under mild reaction conditions (up to 99% *ee* and S/C = 1000). The influence of the substrate on the enantioselectivity and reactivity is investigated, and the most suitable substrate configuration for the highly efficient enantioselective hydrogenation of β-substituted α-aminomethylacrylates under the Rh–Duphos system is reported. The current protocol provides a very practical, facile, and scalable method for the preparation of heterocyclic and alicyclic β²-amino acids and their derivatives.

Keywords: amino acids · asymmetric catalysis · heterocycles · hydrogenation · rhodium

Introduction

Enantiopure β-amino acids have drawn extensive attention because they can be used as important building blocks for the construction of new peptidomimetics and are key structural units in some natural products and pharmaceuticals. The β²-amino acid (α-substituted β-amino acid) subclass is particularly attractive as the alkyl substituent at the α-position of the scaffold favors the folded conformations in the β-peptides.[1–5] In this amino acid family, the heterocyclic and alicyclic amino acids and their derivatives are very interesting because of their unique structures and properties.[6a,b] In the past decade, several stoichiometric[7a,8c,d] and catalytic methods such as asymmetric hydrogenation,[7b,c,9] asymmetric transfer hydrogenation,[7d] carbenoid-induced C–H activation,[7e] and enantioselective H-atom transfer[7f] have been investigated for the preparation of β²-amino acids and their derivatives. However, low reactivities, poor stability and enantioselectivities were often met when a heteroatom or an alicyclic ring was part of the substrate.[7] Among all these catalytic asymmetric protocols, the hydrogenation of prochiral substrates appears to be a preferable method for achieving high efficiency and atom economy. Although asymmetric hydrogenation has been successfully applied for the synthesis of some heterocyclic and alicyclic α-, β³-, γ-amino acids and their derivatives during the past two decades,[6] its use in the preparation of the chiral β²-counterparts has been rarely reported. One example has been recently reported by Zheng and co-workers, whose method provided the hydrogenated product methyl 2-(phthalimidomethyl)-3-(2-thienyl)-propanoate in only 60% conversion and 55.4% *ee* (85 atm, S/C = 25, 36 h).[7b] During the preparation of this manuscript, Holz, Börner and co-workers reported the hydrogenation of dehydro β²-amino acid derivatives with a furyl or thienyl group. In their study, the incomplete conversion of the thienyl-based substrate was ascribed to the negative effect of the sulfur atom in the heteroaromatic cycle on the active metal.[7c] To the best of our knowledge, no report has been disclosed on the preparation of enantioenriched acyclic β²-amino acids and their derivatives by an enantioselective hydrogenation. We have previously developed a synthetic strategy for the preparation of β²-amino acids and their derivatives that possess an aromatic ring or aliphatic chain at the β-position with remarkable activities (S/C up to 10000) and excellent enantioselectivities (up to 99.5% *ee*).[9g,h] Herein, we disclose its further application in the synthesis of novel chiral β²-amino acid derivatives with heterocyclic or alicyclic rings. The corresponding free β²-amino acids can be prepared through ester group cleavage by employing LiOH and subsequent hydrogenolysis with Pd/C.[9h]

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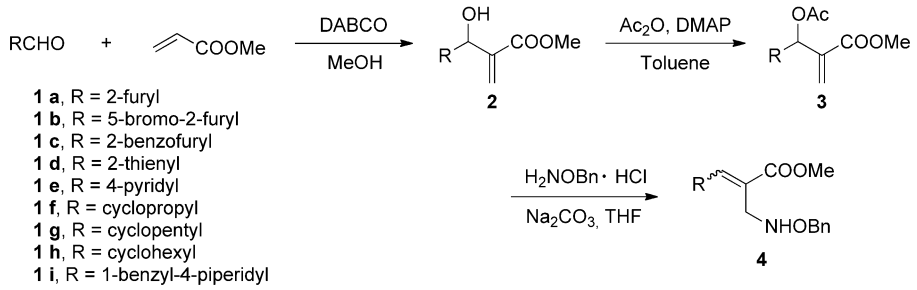
Results and Discussion

As reported in our previous studies, prochiral substrates **4** were generally prepared in a three-step transformation by a Baylis–Hillman reaction, *O*-acetylation, and a subsequent allylic amination (Scheme 1).[9h,10] Among the substrates



Scheme 1. Synthesis of prochiral substrates **4**.

shown in Scheme 1, the acetylation product 4-pyridyl acetate **3e** was found to be unstable and decomposed quickly even when it was kept under nitrogen and at a low temperature. To circumvent this problem, we attempted to synthesize **4e** from **2e** in a one-pot reaction. Upon completion of the acetylation reaction, the amination reaction was allowed to proceed in the same reaction vessel successively without separation of **3e**, and **4e** was isolated successfully in 30% yield. The *E*- and *Z*-isomers of **4c**–**4e** and **4i** were simply separated by silica-gel column chromatography.[11] For **4a**, **4b**, **4f**–**4h**, the two geometric isomers were inseparable and the corresponding mixture was directly used in the ensuing catalytic hydrogenation (Table 1).

Table 1. Synthesis of prochiral substrates **4**.[a]

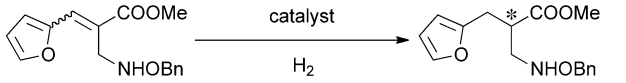
Entry	R	Yield [%][b]	Yield of (*E*)-**4** [%][b]	Yield of (*Z*)-**4** [%][b]
1	2-furyl (**4a**)	79 (*E*/*Z*=5:1)		
2	5-bromo-2-furyl (**4b**)	91 (*E*/*Z*=10:3)		
3	2-benzofuryl (**4c**)	86	74	12
4	2-thienyl (**4d**)	89	70	19
5[c]	4-pyridyl (**4e**)	30	30	trace
6	cyclopropyl (**4f**)	63 (*E*/*Z*=10:9)		
7	cyclopentyl (**4g**)	82 (*E*/*Z*=7:10)		
8	cyclohexyl (**4h**)	91 (*E*/*Z*=3:5)		
9	1-benzyl-4-piperidyl (**4i**)	96	33	63

[a] Reaction conditions: **3**, Na_2CO_3, and *O*-benzylhydroxylamine hydrochloride were allowed to stir in THF at room temperature under N_2. [b] Yield of isolated product. [c] One-pot synthesis from **2e**.

Following the same procedures as those in our previous studies,[9g,h] the asymmetric hydrogenation of a mixture of *E*/*Z*-**4a** was performed at room temperature under low-pressure hydrogenation (50 psi) using 1 mol% [Rh(Et-Duphos)(cod)]BF_4 (cod = cyclooctadiene) as the catalyst. The catalyst system was found to be highly effective and enantioselective as **5a** was obtained in >99% yield and 94% *ee* (Table 2, entry 7). In contrast, both the reactivity and enantioselectivity were low when binap (2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl), 1,2-bis(2,5-dimethylphospholanyl)-benzene (Me-Duphos), or *i*Pr-Duphos (*i*Pr-Duphos: 1,2-bis(2,5-diisopropylphospholanyl)benzene) was used instead (Table 2, entries 1, 2, 4–6, and 8). *i*PrOH was found to be the best solvent to achieve high enantioselectivity and high reactivity. Having established the optimized reaction conditions, a series of novel heterocyclic or alicyclic β^2-amino acid derivatives **5** were prepared in high yields with outstanding reactivities and enantioselectivities. The results are shown in Table 3.

As shown in Table 3, except for **4b** and **4e** with a 5-bromo-2-furyl and 4-pyridyl group as the R group, respectively, all the *E*/*Z*- and *E*-substrates in the current study showed high reactivities towards hydrogenation. The reactions were complete within a short period of time (maximum 2 h) at room temperature under low-pressure hydrogenation (50 psi) in the presence of 1 mol% [Rh(Et-Duphos)(cod)]BF_4 catalyst (Table 3, entries 1, 6, 10, 14, 15, 18, 19, and 22). Notably, (*E*/*Z*)-**4a**, (*E*)-**4c**, and (*E*/*Z*)-**4f**–**4h** were fully converted into the desired products within only 20 min (Table 3, entries 1, 6, 15, 18, and 19). Interestingly, (*E*)-**4d** was transformed completely into the corresponding product **5d** with excellent enantioselection within 120 min (Table 3, entry 10; 98% *ee*). The catalytic result is very different from and significantly better than that reported in the literature for the hydrogenation of other analogues.[7b,c] This suggests that the undesired interaction between the active metal and the sulfur atom of the substrate does not exist in our catalytic system. Hydrogenation of (*E*)-**4i** was also achieved with excellent enantioselectivity and reactivity (Table 3, entry 22). With an alicyclic substituent at the β-position of the carbon–carbon double bond, direct hydrogenation of the mixture of *E*/*Z*-isomers of **4f**–**4h** led to excellent enantioselectivities, thereby yielding **5f**–**5h** in 99%, 98%, and 96% *ee*, respectively (Table 3, entries 15, 18, and 19). By further increasing the S/C to 1,000, full conversion of **4f** and **4h** was achieved with reaction times of 180 and 120 min, respectively. These reactivities were not only significantly better than those substrates with an alkyl chain group but also superior to the substrates bearing a phenyl group[9g] (Table 3, entries 17 and 20). The presence of the alicyclic substituent is beneficial to the substrate activity. In comparison with substrates **4c**, **4d**, and **4f**–**4i**, hydrogenation of (*E*/*Z*)-**4a** with a 2-furyl sub-

Table 2. Screening of the ligands and optimization of the reaction conditions.[a]



(*E*/*Z*)-**4a** **5a**

Entry	Catalyst	Solvent	*t* [min]	Yield [%][b]	*ee* [%][c]
1	[Rh(*R*)-binap(cod)]BF_4	MeOH	600	trace	nd
2	[Rh(*R*,*R*)-Me-Duphos-(cod)]BF_4	MeOH	600	4[d]	76 (+)
3	[Rh(*S*,*S*)-Et-Duphos-(cod)]BF_4	MeOH	20	>99	90 (−)
4	[Rh(*R*,*R*)-*i*Pr-Duphos-(cod)]BF_4	MeOH	600	3[d]	42 (−)
5	[Rh(*R*)-binap(cod)]BF_4	*i*PrOH	600	trace	nd
6	[Rh(*R*,*R*)-Me-Duphos-(cod)]BF_4	*i*PrOH	600	1[d]	nd
7	[Rh(*S*,*S*)-Et-Duphos-(cod)]BF_4	*i*PrOH	20	>99	94 (−)
8	[Rh(*R*,*R*)-*i*Pr-Duphos-(cod)]BF_4	*i*PrOH	600	<1[d]	nd
9	[Rh[(*S*,*S*)-Et-Duphos-(cod)]BF_4	THF	20	46[d]	93 (−)
10	[Rh[(*S*,*S*)-Et-Duphos-(cod)]BF_4	THF	120	99	94 (−)
11	[Rh[(*S*,*S*)-Et-Duphos-(cod)]BF_4	CH_2Cl_2	20	23[d]	nd
12	[Rh[(*S*,*S*)-Et-Duphos-(cod)]BF_4	CH_2Cl_2	300	99	91 (−)
13	[Rh[(*S*,*S*)-Et-Duphos-(cod)]BF_4	Toluene	20	9[d]	nd
14	[Rh[(*S*,*S*)-Et-Duphos-(cod)]BF_4	Toluene	300	52[d]	88 (−)

[a] All reactions were run at room temperature, solvent = 1.5 mL, substrate = 0.1 mmol, substrate/catalyst (S/C) = 100, hydrogen pressure = 50 psi; nd = not determined. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC analysis (Chiralcel OD-H). [d] The conversions were determined by ^1H NMR spectroscopy.

stituent had a slightly lower enantioselectivity (94% *ee*, Table 3, entry 1), but our system still has a remarkable advantage over other reported methods for the hydrogenation of analogues (mixture of *E*/*Z*-isomers, 94% *ee*, 20 min vs pure *E*-substrate, 90% *ee*, 5 h).[7c] Changing the furyl group of **4a** into a 5-bromo furyl group ((*E*/*Z*)-**4b**) led to a significant decrease in the reaction activity (Table 3, entry 4). By raising the hydrogen pressure to 1450 psi and using 2 mol% [Rh(Et-Duphos)(cod)]BF_4 as the catalyst, product **5b** was finally afforded in 99% yield with 90% *ee* in 72 h (Table 3, entry 5). Presumably the steric influence of the bromine atom had an negative effect on the reactivity.

An interesting phenomenon was also noticed. Although pyridyl, furyl, and thienyl are all aromatic heterocycles attached to substrates **4e**, **4a**, and **4d**, respectively, the hydrogenation behavior of **4e** was significantly different from those of **4a** and **4d**. No reaction took place for (*E*)-**4e** under the general reaction conditions (Table 3, entry 11). By increasing the hydrogen pressure or the amount of catalyst, the reactivity increased but it was still far from satisfactory (Table 3, entries 12 and 13). Gratifyingly, favorable changes occurred after the addition of HBF_4 during the hydrogenation. Product **5e** was readily afforded in >99% yield and 93% *ee* within 60 min (Table 3, entry 14). This result might be ascribed to the partial complexation of the bare nitrogen atom of the 4-pyridyl group to the catalyst, thus causing a significant decrease in the catalytic activity. Protonation of HBF_4 to the basic pyridyl nitrogen atom of (*E*)-**4e** could inhibit the unfavorable nitrogen coordination to the catalyst.

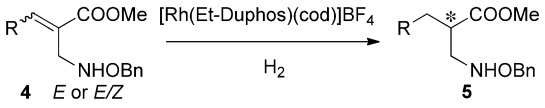
In our previous work,[9g,h] *Z*-α-aminomethylacrylates with an aromatic ring showed lower reactivity and enantiodifferentiation than the corresponding *E*-isomers. Similar phenomena were also observed in the reaction of heteroaromatic substrates **4c** and **4d** (Table 4, entries 1–3). However, the exact behavior of the single isomer with an alkyl R group has not been investigated before because the pure *E*- or *Z*-isomeric substrate could not be obtained conveniently. By introducing a large alkyl group (1-benzyl-4-piperidyl) into the substrates, (*E*)- and (*Z*)-**4i** were successfully separated by silica-gel column chromatography. Furthermore, (*Z*)-**4i** was found to be more reactive than (*E*)-**4i**. The obtained enantioselectivities were also comparable (Table 4, entry 5 vs. Table 3, entry 22). Thus, hydrogenation of a mixture of (*E*/*Z*)-**4i** gave an excellent result (Table 4, entry 8). This outcome was very different from that observed in the hydrogenation of the aromatic and heteroaromatic moieties. On the basis of this result, a general speculation could be made for the hydrogenation of β-substituted α-aminomethylacrylates under the Rh–Duphos system: the reactivity and enantioselectivity are high for both *E*- and *Z*-isomers if the R group of the prochiral substrate is not conjugated with the carbon–carbon double bond of the acrylates. The hydrogention results for the mixture of *E*/*Z*-isomers bearing the aliphatic and alicyclic substituents all supported this hypothesis (Table 3, entries 15–20; Table 4, entry 8 and the previous studies[9h]). On the contrary, the *Z*-α-aminomethylacrylate with an aromatic or heteroaromatic R group provided less favorable results in comparison with the corresponding *E*-isomer. That is, only the pure *E*-isomers were good for achieving excellent reactivities and enantioselectivities.

Other parameters such as reaction temperature and H_2 pressure were also examined. It was found that the enantioselectivity was unaffected by H_2 pressure (Table 4, entry 6 vs. entry 5), but the high H_2 pressure was beneficial for the reactivity. In separate observations, the reactions performed at higher temperatures almost always yielded more side products as compared to those performed at ambient temperature.

Conclusions

In summary, we have demonstrated an efficient synthetic route to α-aminomethylacrylates possessing β-heterocyclic or alicyclic groups. The prochiral precursors were easily accessible by the Baylis–Hillman reaction of aldehydes with methyl acrylate followed by the acetylation of the resulting allylic alcohols and S_N2'-type amination of the allylic acetates. The corresponding novel β^2-amino acid derivatives were prepared in high yields and with excellent enantiose-

Table 3. Hydrogenation of *E*/*Z*- and *E*-α-aminomethylacrylates.[a]

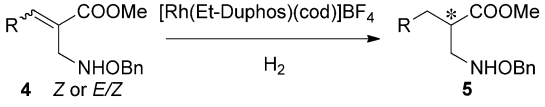


4 *E* or *E*/*Z* 5

Entry	R (Substrate)	S/C	*P* [psi]	*t* [min]	Yield [%][b]	*ee* [%][c]
1	2-furyl (*E*/*Z*)-**4a**	100	50	20	>99	94 (−)
2	2-furyl (*E*/*Z*)-**4a**	500	50	240	>99	93 (−)
3	2-furyl (*E*/*Z*)-**4a**	1000	50	96 h	>99	93 (−)
4	5-bromo-2-furyl (*E*/*Z*)-**4b**	100	50	60	trace	nd
5	5-bromo-2-furyl (*E*/*Z*)-**4b**	50	1450	72 h	99	90 (−)
6	2-benzofuryl (*E*)-**4c**	100	50	20	>99	98 (−)
7	2-benzofuryl (*E*)-**4c**	500	50	120	44[d]	97 (−)
8	2-benzofuryl (*E*)-**4c**	500	50	240	>99	98 (−)
9	2-thienyl (*E*)-**4d**	100	50	60	88[d]	98 (−)
10	2-thienyl (*E*)-**4d**	100	50	120	>99	98 (−)
11	4-pyridyl (*E*)-**4e**	100	50	120	trace	nd
12	4-pyridyl (*E*)-**4e**	100	1450	96 h	91[d]	90 (−)
13	4-pyridyl (*E*)-**4e**	50	1450	144 h	98	90 (−)
14[e]	4-pyridyl (*E*)-**4e**	100	50	60	>99	93 (−)
15	cyclopropyl (*E*/*Z*)-**4f**	100	50	20	>98	99 (−)
16	cyclopropyl (*E*/*Z*)-**4f**	500	50	60	>99	98 (−)
17	cyclopropyl (*E*/*Z*)-**4f**)	1000	50	180	>99	99 (−)
18	cyclopentyl (*E*/*Z*)-**4g**	100	50	20	>99	98 (−)
19	cyclohexyl (*E*/*Z*)-**4h**	100	50	20	99	96 (−)
20	cyclohexyl (*E*/*Z*)-**4h**	1000	50	120	>99	96 (−)
21	1-benzyl-4-piperidyl (*E*)-**4i**	100	50	60	84[d]	97 (−)
22	1-benzyl-4-piperidyl (*E*)-**4i**	100	50	120	>99	98 (−)

[a] Catalyst = [Rh(*S*,*S*)-Et-Duphos(cod)]BF_4, *i*PrOH = 1.5 mL, substrate = 0.1 mmol, room temperature; nd = not determined. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC analysis (Chiralcel OD-H). [d] The conversions were determined by ^{1}H NMR spectroscopy. [e] The hydrogenation was conducted in the presence of HBF_4 (1.5 equiv).

Table 4. Hydrogenation of *Z*-α-aminomethylacrylates and (*E*/*Z*)-**4i**.[a]



4 *Z* or *E*/*Z* 5

Entry	R (Substrate)	S/C	*P* [psi]	*t* [min]	Yield [%][b]	*ee* [%][c]
1	2-benzofuryl (*Z*)-**4c**	100	50	20	>99	11 (−)
2	2-thienyl (*Z*)-**4d**	100	50	120	30[d]	nd
3	2-thienyl (*Z*)-**4d**	100	1000	60	99	60 (−)
4	1-benzyl-4-piperidyl (*Z*)-**4i**	100	50	20	74[d]	nd
5	1-benzyl-4-piperidyl (*Z*)-**4i**	100	50	60	>99	97 (−)
6	1-benzyl-4-piperidyl (*Z*)-**4i**	100	1000	20	>99	97 (−)
7	1-benzyl-4-piperidyl (*Z*)-**4i**	500	1000	36 h	>99	97 (−)
8	1-benzyl-4-piperidyl (*E*/*Z*)-**4i**	100	50	120	>99	97 (−)

[a] Catalyst = [Rh(*S*,*S*)-Et-Duphos(cod)]BF_4, *i*PrOH = 1.5 mL, substrate = 0.1 mmol, room temperature; nd = not determined. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC analysis (Chiralcel OD-H). [d] The conversions were determined by ^{1}H NMR spectroscopy.

lectivities by catalytic asymmetric hydrogenation of the prochiral substrates (up to 99% *ee*, S/C = 1000). The relationship between the nature of the substrate and catalytic behavior was further explored. In combination with our previous research, a general method for the synthesis of β^2-amino acids and their derivatives with a broad scope of aromatic, aliphatic, alicyclic, and heterocyclic substituents was established. The simple and highly efficient approach to the new β^2-amino acid derivatives provides an exceptional platform for their further applications.

Experimental Section

General Information

^{1}H and ^{13}C NMR spectra were recorded on a 300 and 75 MHz FT-NMR spectrometer. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. HR-MS was carried out on an ESI FT-ICR mass spectrometer. Melting points determined are uncorrected. Optical rotations were recorded on a polarimeter in a 10 cm cell. HPLC analysis was performed using a Daicel Chiralpak OD-H column. [Rh(*S*,*S*)-Et-Duphos-(cod)]BF_4 was purchased from Strem Chemicals (Newburyport, USA). *i*PrOH was distilled from calcium hydride before use. Ethyl acetate and petroleum ether (boiling range 60–90 °C) used for column chromatography were purchased from Shanghai Titanchem Co. Ltd (Shanghai, China).

General Procedure for the Synthesis of ***2***

A mixture of aldehyde **1** (20 mmol) and 1,4-diazabicyclo-[2.2.2]octane (DABCO; 2 mmol) in MeOH (40 mL) was added to methyl acrylate (60 mmol). The solution was stirred at room temperature until the reaction was complete (monitored by TLC). The mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. Products were purified by column chromatography (SiO_2; ethyl acetate/petroleum ether 1:5).

*Methyl 2-(furan-2-yl(hydroxy)methyl)acrylate (**2a**)*[12a]

Light yellow oil: 2.81 g, 77%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 1H), 6.36 (s, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 5.93 (s, 1H), 5.57 (d, *J* = 6.2 Hz, 1H), 3.74 (s, 3H), 3.29 ppm (d, *J* = 6.5 Hz, 1H).

*Methyl 2-((5-bromofuran-2-yl)(hydroxy)methyl)acrylate (**2b**)*[12b]

Light brown oil: 1.83 g, 35%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.41 (t, *J* = 0.7 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 3.3, 0.6 Hz, 1H), 5.99 (t, *J* = 0.7 Hz, 1H), 5.53 (d, *J* = 6.9 Hz, 1H), 3.78 (s, 3H), 3.17 ppm (d, *J* = 6.9, 1.0 Hz, 1H).

*Methyl 2-(benzofuran-2-yl(hydroxy)methyl)acrylate (**2c**)*

Light yellow oil: 4.51 g, 97%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.46 (m, 1H), 7.43–7.38 (m, 1H), 7.26–7.12 (m, 2H), 6.61 (s, 1H), 6.41 (s, 1H), 6.00 (s, 1H), 5.69 (d, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 3.69 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 156.9, 155.1, 139.1, 128.3, 127.8, 124.5, 123.1, 121.4, 111.6, 104.2, 68.0, 52.5 ppm; HR-MS (ESI): *m*/*z* calcd. for $C_{13}H_{12}O_4Na^+$ $[M+Na]^+$: 255.0628, found 255.0623.

*Methyl 2-(hydroxy(2-thienyl)methyl)acrylate (**2d**)*[12c]

Light yellow oil: 3.49 g, 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.18 (m, 1H), 6.94–6.89 (m, 2H), 6.32 (s, 1H), 5.95 (s, 1H), 5.73 (d, *J* = 5.7 Hz, 1H), 3.79 (d, *J* = 6.0 Hz, 1H), 3.70 ppm (s, 3H).

*Methyl 2-(hydroxy(pyridin-4-yl)methyl)acrylate (**2e**)*[12d]

White solid: 3.36 g, 87%, M.p. 139–140 °C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 8.48 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.29 (dd, *J* = 4.5, 1.5 Hz, 2H), 6.24 (s, 1H), 6.07 (d, *J* = 4.5 Hz, 1H), 6.00 (t, *J* = 1.2 Hz, 1H), 5.44 (d, *J* = 3.2 Hz, 1H), 3.61 ppm (s, 3H).

*Methyl 2-(cyclopropyl(hydroxy)methyl)acrylate (**2f**)*

Colorless oil: 1.87 g, 60%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23 (d, J = 1.0 Hz, 1H), 5.91–5.88 (m, 1H), 3.79 (s, 3H), 3.75–3.68 (m, 1H), 2.85 (d, J = 5.5 Hz, 1H), 1.21–1.07 (m, 1H), 0.68–0.40 (m, 3H), 0.33–0.23 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 142.1, 125.2, 75.1, 52.2, 16.6, 3.9, 3.1 ppm; HR-MS (ESI): m/z calcd. for $C_8H_{12}O_3Na^+$ $[M+Na]^+$: 179.0679; found 179.0679.

*Methyl 2-(cyclopentyl(hydroxy)methyl)acrylate (**2g**)*

Colorless oil: 2.43 g, 66%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.19 (s, 1H), 5.77 (s, 1H), 4.15 (t, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.01 (d, J = 7.1 Hz, 1H), 2.26–2.11 (m, 1H), 1.81–1.44 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 142.2, 125.6, 75.9, 52.0, 45.0, 29.9, 29.0, 25.9, 25.8 ppm; HR-MS (ESI): m/z calcd. for $C_{10}H_{16}O_3Na^+$ $[M+Na]^+$: 207.0992; found 207.0999

*Methyl 2-(cyclohexyl(hydroxy)methyl)acrylate (**2h**)[12e]*

Colorless oil: 2.58 g, 65%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.24 (d, J = 1.3 Hz, 1H), 5.74 (t, J = 1.1 Hz, 1H), 4.09 (d, J = 6.9 Hz, 1H), 3.77 (s, 3H), 2.80 (br s, 1H), 1.77–1.52 (m, 5H), 1.30–0.89 ppm (m, 6H).

*Methyl 2-((1-benzylpiperidin-4-yl)(hydroxy)methyl)acrylate (**2i**)*

Light yellow oil: 2.49 g, 43%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 5H), 6.25 (s, 1H), 5.73 (s, 1H), 4.06 (d, J = 7.7 Hz, 1H), 3.77 (s, 3H), 3.49 (s, 2H), 2.99–2.83 (m, 2H), 1.92 (dt, J = 5.9, 3.6 Hz, 3H), 1.67–1.53 (m, 1H), 1.48–1.22 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 141.2, 138.3, 129.5, 128.3, 127.1, 126.7, 76.3, 63.6, 53.8, 53.7, 52.2, 41.1, 29.3, 28.2 ppm; HR-MS (ESI): m/z calcd. for $C_{17}H_{24}NO_3^+$ $[M+H]^+$: 290.1751; found 290.1752.

*General Procedure for the Synthesis of **3***

Acetic anhydride (18 mmol) was added dropwise into a mixture of **2** (15 mmol) and 4-dimethylaminopyridine (DMAP; 1.5 mmol) in toluene (20 mL) over 30 min at 0–5 °C. The resulting solution was allowed to warm to room temperature in 1 h. After stirring for 1 h at room temperature, the reaction mixture was cooled to 0–5 °C, and 1 N HCl (5 mL) was added over 20 min. The organic layer was separated and washed sequentially with water, saturated aqueous sodium bicarbonate, and water. The organic layer was concentrated to afford **3** as a colorless liquid. Products were purified by column chromatography (SiO_2; ethyl acetate/petroleum ether 1:5).

*Methyl 2-(acetoxy(furan-2-yl)methyl)acrylate (**3a**)[12f]*

Light yellow oil: 3.09 g, 92%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 1H), 6.75–6.71 (m, 1H), 6.45 (s, 1H), 6.34–6.29 (m, 2H), 6.00–5.97 (m, 1H), 3.72 (s, 3H), 2.10 ppm (s, 3H).

*Methyl 2-(acetoxy(5-bromofuran-2-yl)methyl)acrylate (**3b**)*

Light brown oil: 4.14 g, 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (s, 1H), 6.42 (d, J = 0.5 Hz, 1H), 6.25 (d, J = 3.3 Hz, 1H), 6.20 (d, J = 3.3 Hz, 1H), 5.98–5.96 (m, 1H), 3.69 (s, 3H), 2.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 164.9, 152.4, 136.5, 127.3, 122.9, 112.7, 66.0, 52.4, 21.2 ppm; HR-MS (ESI): m/z calcd. for $C_{11}H_{11}BrO_5Na^+$ $[M+Na]^+$: 324.9682; found 324.9690.

*Methyl 2-(acetoxy(benzofuran-2-yl)methyl)acrylate (**3c**)*

Light yellow oil: 4.03 g, 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.19 (dt, J = 14.7, 7.1 Hz, 2H), 6.89 (s, 1H), 6.70 (s, 1H), 6.51 (s, 1H), 6.06 (s, 1H), 3.69 (s, 3H), 2.10 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 165.1, 155.3, 153.1, 136.8, 127.9, 127.7, 125.1, 123.2, 121.6, 111.7, 106.7, 66.8, 52.5, 21.2 ppm; HR-MS (ESI): m/z calcd. for $C_{15}H_{14}O_5Na^+$ $[M+Na]^+$: 297.0733; found 297.0739.

*Methyl 2-(acetoxy(2-thienyl)methyl)acrylate (**3d**)[12f]*

Light yellow oil: 3.53 g, 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (dd, J = 5.1, 1.2 Hz, 1H), 7.07–7.04 (m, 1H), 6.97–6.91 (m, 2H), 6.42 (s, 1H), 6.02–5.96 (m, 1H), 3.74 (s, 3H), 2.11 ppm (s, 3H).

*Methyl 2-(acetoxy(pyridin-4-yl)methyl)acrylate (**3e**)*

Brown oil: 0.18 g, 5%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (dd, J = 4.5, 1.6 Hz, 2H), 7.34–7.30 (m, 2H), 6.63 (s, 1H), 6.46–6.44 (m, 1H), 5.92 (dd, J = 1.3, 0.6 Hz, 1H), 3.73 (s, 3H), 2.15 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 165.0, 149.9, 147.2, 138.7, 127.3, 122.2, 72.0, 52.3, 21.1 ppm; HR-MS (ESI): m/z calcd. for $C_{12}H_{14}NO_4^+$ $[M+H]^+$: 236.0917; found 236.0919.

*Methyl 2-(acetoxy(cyclopropyl)methyl)acrylate (**3f**)[12g]*

Colorless oil: 2.71 g, 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.30 (d, J = 0.8 Hz, 1H), 5.89 (t, J = 1.0 Hz, 1H), 5.09 (d, J = 7.9 Hz, 1H), 3.77 (s, 3H), 2.08 (s, 3H), 1.26–1.12 (m, 1H), 0.60–0.53 (m, 2H), 0.49–0.37 ppm (m, 2H).

*Methyl 2-(acetoxy(cyclopentyl)methyl)acrylate (**3g**)*

Colorless oil: 3.09 g, 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.26 (d, J = 1.0 Hz, 1H), 5.76 (t, J = 1.0 Hz, 1H), 5.52 (d, J = 7.0 Hz, 1H), 3.77 (s, 3H), 2.36–2.22 (m, 1H), 2.06 (s, 3H), 1.68–1.25 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 166.0, 140.3, 125.9, 74.9, 52.2, 43.6, 29.1, 28.5, 25.8, 25.5, 21.3 ppm; HR-MS (ESI): m/z calcd. for $C_{12}H_{18}O_4Na^+$ $[M+Na]^+$: 249.1097; found 249.1099.

*Methyl 2-(acetoxy(cyclohexyl)methyl)acrylate (**3h**)[12h]*

Colorless oil: 3.35 g, 93%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.30 (s, 1H), 5.70 (s, 1H), 5.44 (d, J = 5.8 Hz, 1H), 3.77 (s, 3H), 2.07 (s, 3H), 1.78–1.58 (m, 6H), 1.25–0.97 ppm (m, 5H).

*Methyl 2-(acetoxy(1-benzylpiperidin-4-yl)methyl)acrylate (**3i**)*

Light yellow oil: 4.47 g, 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.16 (m, 5H), 6.29 (d, J = 1.0 Hz, 1H), 5.69 (d, J = 1.0 Hz, 1H), 5.49 (d, J = 5.4 Hz, 1H), 3.74 (s, 3H), 3.46 (s, 2H), 2.93–2.83 (m, 2H), 2.05 (s, 3H), 1.97–1.81 (m, 2H), 1.69–1.35 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 165.8, 138.9, 138.5, 129.3, 128.3, 127.1, 126.4, 75.1, 63.5, 53.8, 53.7, 52.3, 39.6, 28.9, 27.3, 21.3 ppm; HR-MS (ESI): m/z calcd. for $C_{19}H_{26}NO_4^+$ $[M+H]^+$: 332.1856; found 332.1854.

*General Procedure for the Synthesis of **4***

A mixture of **3** (14.5 mmol), Na_2CO_3 (43.5 mmol), and *O*-benzylhydroxylamine hydrochloride (43.5 mmol) in THF (20 mL) was allowed to stir at room temperature under N_2 until the reaction was complete (as monitored by TLC). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate (25 mL). The ethyl acetate layer was concentrated to afford a colorless liquid. The crude material was purified by column chromatography (SiO_2; acetone/petroleum ether 1:20) to afford **4** (*E*-isomer, *Z*-isomer, and an *E*/*Z*-isomeric mixture).

*(E/Z)-Methyl 2-((benzyloxyamino)methyl)-3-(furan-2-yl)acrylate ((E/Z)-**4a**)*

Light yellow oil: 3.29 g, 79%, E/Z = 5:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 0.83×1H), 7.49 (s, 0.83×1H), 7.40 (d, J = 1.7 Hz, 0.17×1H), 7.36–7.19 (m, 5H), 7.00 (d, J = 3.5 Hz, 0.17×1H), 6.68 (s, 0.17×1H), 6.64 (d, J = 3.5 Hz, 0.83×1H), 6.45 (dd, J = 3.5, 1.8 Hz, 0.83×1H), 6.42 (dd, J = 3.5, 1.8 Hz, 0.17×1H), 6.04 (br s, 1H), 4.71 (s, 0.83×2H), 4.69 (s, 0.17×2H), 4.23 (s, 0.83×2H), 3.78 (s, 0.17×3H), 3.77 (s, 0.83×3H), 3.76 ppm (s, 0.17×2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 168.0, 151.1, 150.4, 145.2, 143.8, 138.2, 138.1, 129.0, 128.7, 128.0, 127.9, 126.9, 125.0, 124.3, 117.3, 114.7, 112.5, 112.4, 76.4, 75.9, 56.7, 52.4, 52.0, 48.6 ppm; HR-MS (ESI): m/z calcd. for $C_{16}H_{18}NO_4^+$ $[M+H]^+$: 288.1230; found 288.1237.

*(E/Z)-Methyl 2-((benzyloxyamino)methyl)-3-(5-bromofuran-2-yl) acrylate ((E/Z)-**4b**)*

Light yellow oil: 4.83 g, 91%, E/Z=10:3; ^{1}H NMR (300 MHz, $CDCl_3$,): δ=7.39 (s, 0.77×1H), 7.33–7.19 (m, 5H), 7.00 (d, J=3.5 Hz, 0.23×1H), 6.60 (s, 0.23×1H), 6.55 (d, J=3.5 Hz, 0.77×1H), 6.37 (d, J=3.5 Hz, 0.77×1H), 6.34 (d, J=3.5 Hz, 0.23×1H), 5.92 (brs, 1H), 4.72 (s, 0.77×2H), 4.67 (s, 0.23×2H), 4.17 (s, 0.77×2H), 3.77 (s, 0.23×3H), 3.75 (s, 0.77×3H), 3.74 ppm (d, J=0.9 Hz, 0.23×2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.1, 167.6, 152.9, 152.5, 138.2, 138.0, 128.7, 128.5, 128.0, 127.9, 126.0, 125.7, 125.4, 124.8, 119.2, 117.2, 114.4, 114.2, 76.4, 75.9, 56.4, 52.5, 52.1, 48.5 ppm; HR-MS (ESI): m/z calcd. for $C_{16}H_{17}BrNO_4^+$ $[M+H]^+$: 366.0335; found 366.0336.

*(E)-Methyl 3-(benzofuran-2-yl)-2-(((benzyloxy)amino)methyl) acrylate ((E)-**4c**)*

White solid: 3.62 g, 74%, M.p. 59–60°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.61 (s, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.46 (d, J=8.2 Hz, 1H), 7.33 (t, J=7.6 Hz, 1H), 7.28–7.16 (m, 6H), 6.96 (s, 1H), 6.03 (brs, 1H), 4.74 (s, 2H), 4.39 (s, 2H), 3.80 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.2, 155.9, 152.6, 138.1, 129.2, 128.5, 128.1, 127.9, 127.7, 126.7, 123.7, 122.0, 113.6, 111.8, 75.9, 52.7, 48.6 ppm; HR-MS (ESI): m/z calcd. for $C_{20}H_{19}NO_4Na^+$ $[M+Na]^+$: 360.1206; found 360.1200.

*(Z)-Methyl 3-(benzofuran-2-yl)-2-(((benzyloxy)amino)methyl) acrylate ((Z)-**4c**)*

Light yellow oil: 0.59 g, 12%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.57–7.51 (m, 1H), 7.39 (d, J=8.4 Hz, 1H), 7.34–7.24 (m, 6H), 7.22–7.15 (m, 1H), 7.13 (s, 1H), 6.71 (s, 1H), 5.79 (brs, 1H), 4.71 (s, 2H), 3.85 (s, 3H), 3.83 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.5, 155.1, 151.7, 137.9, 130.0, 128.7, 128.6, 128.1, 125.8, 124.9, 123.3, 121.9, 111.3, 109.8, 76.6, 56.7, 52.3 ppm; HR-MS (ESI): m/z calcd. for $C_{20}H_{19}NO_4Na^+$ $[M+Na]^+$: 360.1206; found 360.1214.

*(E)-Methyl 2-((benzyloxyamino)methyl)-3-(2-thienyl) acrylate ((E)-**4d**)*

Light yellow oil: 3.08 g, 70%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.93 (s, 1H), 7.47 (d, J=5.1 Hz, 1H), 7.35–7.24 (m, 6H), 7.06 (dd, J=5.1, 3.7 Hz, 1H), 5.98 (brs, 1H), 4.75 (s, 2H), 4.17 (s, 2H), 3.79 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.3, 138.2, 137.7, 136.0, 133.6, 130.4, 128.7, 128.5, 127.9, 127.8, 124.0, 76.3, 52.5, 49.2 ppm; HR-MS (ESI): m/z calcd. for $C_{16}H_{17}NO_3SNa^+$ $[M+Na]^+$: 326.0821; found 326.0829.

*(Z)-Methyl 2-((benzyloxyamino)methyl)-3-(2-thienyl) acrylate ((Z)-**4d**)*

Light yellow oil: 0.84 g, 19%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.45 (d, J=5.1 Hz, 1H), 7.37–7.28 (m, 6H), 7.10 (s, 1H), 7.04 (dd, J=5.1, 3.7 Hz, 1H), 5.88 (brs, 1H), 4.73 (s, 2H), 3.83 (s, 3H), 3.83 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.7, 138.1, 137.8, 134.8, 134.6, 130.8, 128.7, 128.6, 128.0, 126.7, 123.2, 76.4, 57.0, 52.0 ppm; HR-MS (ESI): m/z calcd. for $C_{16}H_{17}NO_3SNa^+$ $[M+Na]^+$: 326.0821; found 326.0827.

*(E)-Methyl 2-((benzyloxyamino)methyl)-3-(pyridin-4-yl)acrylate ((E)-**4e**)*

This compound was directly prepared from compound **2e** through a one-pot synthesis. Light yellow oil: 1.30 g, 30%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.51 (dd, J=4.5, 1.5 Hz, 2H), 7.67 (s, 1H), 7.30–7.21 (m, 7H), 5.72 (brs, 1H), 4.63 (s, 2H), 3.81 (s, 2H), 3.76 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.5, 150.1, 142.5, 140.6, 138.0, 131.5, 128.6, 128.5, 128.1, 123.7, 76.3, 52.7, 48.8 ppm; HR-MS (ESI): m/z calcd. for $C_{17}H_{19}N_2O_3^+$ $[M+H]^+$: 299.1390; found 299.1396.

*(E/Z)-Methyl 2-(((benzyloxy)amino)methyl)-3-cyclopropylacrylate ((E/Z)-**4f**)*

Light yellow oil: 2.39 g, 63%, E/Z=10:9; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.38–7.18 (m, 5H), 6.27 (d, J=10.8 Hz, 0.53×1H), 5.90 (s, 1H), 5.39 (d, J=10.8 Hz, 0.47×1H), 4.69 (s, 0.53×2H), 4.65 (s, 0.47×2H), 3.84 (s, 0.53×2H), 3.73 (s, 0.47×3H), 3.68 (s, 0.53×3H), 3.61 (s, 0.47×2H), 2.67–2.53 (m, 0.47×1H), 1.72–1.58 (m, 0.53×1H), 0.99–0.88 (m, 2H), 0.65–0.59 (m, 0.53×2H), 0.56–0.49 ppm (m, 0.47×2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.0, 167.7, 153.9, 152.9, 138.2, 138.2, 128.7, 128.5, 128.5, 128.4, 127.9, 127.9, 125.0, 124.7, 76.2, 76.1, 56.1, 51.9, 51.6, 48.3, 12.8, 12.2, 9.4, 9.4 ppm; HR-MS (ESI): m/z calcd. for $C_{15}H_{19}NO_3Na^+$ $[M+Na]^+$: 284.1257; found 284.1268.

*(E/Z)-Methyl 2-(((benzyloxy)amino)methyl)-3-cyclopentylacrylate ((E/Z)-**4g**)*

Light yellow oil: 3.44 g, 82%, E/Z=7:10; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.39–7.26 (m, 5H), 6.84 (d, J=10.2 Hz, 0.41×1H), 6.03 (d, J=9.8 Hz, 0.59×1H), 5.86 (s, 1H), 4.68 (s, 0.41×2H), 4.68 (s, 0.59×2H), 3.75 (s, 0.41×2H), 3.73 (s, 0.59×3H), 3.73 (s, 0.41×3H), 3.66 (s, 0.59×2H), 3.43–3.28 (m, 0.59×1H), 2.82–2.67 (m, 0.41×1H), 1.88–1.30 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.0, 167.9, 152.5, 138.2, 138.1, 128.7, 128.5, 128.4, 127.9, 126.2, 125.9, 76.2, 56.3, 52.0, 51.6, 48.2, 40.3, 39.7, 34.0, 33.8, 25.9 ppm; HR-MS (ESI): m/z calcd. for $C_{17}H_{24}NO_3^+$ $[M+H]^+$: 290.1751; found 290.1757.

*(E/Z)-Methyl 2-(((benzyloxy)amino)methyl)-3-cyclohexylacrylate ((E/Z)-**4h**)*

Light yellow oil: 4.00 g, 91%, E/Z=3:5; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25–7.13 (m, 5H), 6.65 (d, J=10.2 Hz, 0.37×1H), 5.84 (d, J=9.7 Hz, 0.63×1H), 5.52 (s, 1H), 4.58 (s, 0.37×2H), 4.57 (s, 0.63×2H), 3.63 (s, 0.37×2H), 3.62 (s, 0.63×3H), 3.60 (s, 0.37×3H), 3.54 (s, 0.63×2H), 2.93–2.78 (m, 0.63×1H), 2.35–2.20 (m, 0.37×1H), 1.64–0.95 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.2, 167.7, 152.8, 152.6, 152.5, 138.1, 138.1, 128.7, 128.5, 127.9, 125.8, 125.6, 76.4, 76.2, 76.1, 56.3, 52.0, 51.7, 48.2, 38.5, 38.0, 32.9, 32.5, 26.3, 26.1, 25.9, 25.8 ppm; HR-MS (ESI): m/z calcd. for $C_{18}H_{26}NO_3^+$ $[M+H]^+$: 304.1907; found 304.1906.

*(E)-Methyl 2-(((benzyloxy)amino)methyl)-3-(1-benzylpiperidin-4-yl)acrylate ((E)-**4i**)*

Light yellow oil: 1.89 g, 33%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35–7.28 (m, 10H), 6.78 (d, J=10.1 Hz, 1H), 5.90 (brs, 1H), 4.68 (s, 2H), 3.74 (s, 2H), 3.74 (s, 3H), 3.53 (s, 2H), 2.92–2.83 (m, 2H), 2.43–2.33 (m, 1H), 1.99 (td, J=11.3, 3.4 Hz, 2H), 1.59–1.47 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.0, 151.2, 138.4, 138.2, 129.4, 128.7, 128.5, 128.4, 128.0, 127.2, 126.6, 76.3, 63.8, 53.2, 52.1, 48.3, 36.2, 31.8 ppm; HR-MS (ESI): m/z calcd. for $C_{24}H_{31}N_2O_3^+$ $[M+H]^+$: 395.2329; found 395.2339.

*(Z)-Methyl 2-(((benzyloxy)amino)methyl)-3-(1-benzylpiperidin-4-yl)acrylate ((Z)-**4i**)*

Light yellow oil: 3.60 g, 63%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.38–7.23 (m, 10H), 5.97 (d, J=9.6 Hz, 1H), 5.81 (brs, 1H), 4.68 (s, 2H), 3.74 (s, 3H), 3.66 (s, 2H), 3.52 (s, 2H), 3.05–2.95 (m, 1H), 2.91 (d, J=11.7 Hz, 2H), 2.06 (td, J=11.6, 2.3 Hz, 2H), 1.78–1.68 (m, 2H), 1.48 ppm (ddd, J=15.6, 12.3, 3.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.6, 151.3, 138.5, 138.1, 129.4, 128.5, 128.5, 128.4, 128.0, 127.2, 126.9, 76.3, 63.8, 56.2, 53.4, 51.7, 36.7, 32.1 ppm; HR-MS (ESI): m/z calcd. for $C_{24}H_{31}N_2O_3^+$ $[M+H]^+$: 395.2329; found 395.2341.

General Procedure for Asymmetric Hydrogenation

The catalyst was added to a solution of the substrate and degassed solvent in a glass-lined stainless steel autoclave under a nitrogen atmosphere. After purging three times with H_2, the autoclave was pressurized to the desired pressure with H_2. The solution was stirred well at the given temperature for the time specified in Table 3 or Table 4. After releasing the hydrogen pressure, the reaction mixture was concentrated. The residue was filtered through a short SiO_2 column with ethyl acetate/petroleum ether (1:1) to remove the catalyst. The filtrate was concentrated. The conversion of the reaction was determined by ^{1}H NMR spectroscopy and HPLC. The enantiomeric excess was determined by chiral HPLC.

*Methyl 3-((benzyloxy)amino)-2-(furan-2-ylmethyl) propanoate (**5a**)*

Light yellow oil: 28.6 mg, 99%; ee=94%; $[\alpha]_D^{20}$=−9.0 (c=1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.23–7.18 (m, 6H), 6.15 (dd, J=3.1, 1.9 Hz, 1H), 5.92 (dd, J=3.2, 0.7 Hz, 1H), 4.56 (s, 2H), 3.54 (s, 3H), 3.06–2.81 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.7, 152.8, 141.7, 137.9, 128.6, 128.5, 128.0, 110.4, 106.8, 76.5, 53.3, 52.1, 43.2, 28.7 ppm; HR-MS (ESI): m/z=290.1376, calcd. for $C_{16}H_{20}NO_4^+$

$[M+H]^+$; found 290.1387. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 4:96, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 35.9 min, t_r(major) = 33.7 min.

*Methyl 3-((benzyloxy)amino)-2-((5-bromofuran-2-yl)methyl) propanoate (**5b**)*

Light yellow oil: 26.3 mg, 99%; *ee* = 90%; $[\alpha]_D^{20} = -3.5$ (c = 3.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5H), 6.16 (d, J = 3.2 Hz, 1H), 6.00 (d, J = 3.2 Hz, 1H), 5.73 (brs, 1H), 4.66 (s, 2H), 3.66 (s, 3H), 3.16–2.86 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 155.0, 137.8, 128.7, 128.6, 128.1, 120.2, 112.0, 109.7, 76.5, 53.2, 52.2, 43.0, 28.9 ppm; HR-MS (ESI): m/z calcd. for $C_{16}H_{18}BrNO_4Na^+$ $[M+Na]^+$: 390.031; found 390.0327. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 4:96, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 41.7 min, t_r(major) = 37.6 min.

*Methyl 3-(benzofuran-2-yl)-2-(((benzyloxy)amino)methyl) propanoate (**5c**)*

Light yellow oil: 33.6 mg, 99%; *ee* = 98% via (*E*)-**4c**, *ee* = 11% via (*Z*)-**4c**; $[\alpha]_D^{20} = -2.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.42 (m, 1H), 7.40–7.35 (m, 1H), 7.31–7.21 (m, 5H), 7.21–7.11 (m, 2H), 6.40 (s, 1H), 5.65 (brs, 1H), 4.65 (s, 2H), 3.64 (s, 3H), 3.22–2.95 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 156.0, 154.9, 137.8, 128.9, 128.7, 128.6, 128.1, 123.8, 122.8, 120.7, 111.1, 103.9, 76.6, 53.4, 52.2, 42.8, 29.2 ppm; HR-MS (ESI): m/z calcd. for $C_{20}H_{22}NO_4^+$ $[M+H]^+$: 340.1543; found 340.1549. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 30:70, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 13.5 min, t_r(major) = 10.3 min.

*Methyl 3-((benzyloxy)amino)-2-((2-thienyl)methyl) propanoate (**5d**)*

Light yellow oil: 30.2 mg, 99%; *ee* = 98% via (*E*)-**4d**, *ee* = 60% via (*Z*)-**4d**; $[\alpha]_D^{20} = -6.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5H), 7.11 (dd, J = 5.1, 1.2 Hz, 1H), 6.88 (dd, J = 5.1, 3.4 Hz, 1H), 6.77 (dd, J = 3.4, 1.0 Hz, 1H), 4.65 (s, 2H), 3.64 (s, 3H), 3.19–3.03 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 141.1, 137.8, 128.7, 128.6, 128.1, 127.1, 126.0, 124.2, 76.5, 53.2, 52.1, 46.1, 30.4 ppm; HR-MS (ESI): m/z calcd. for $C_{16}H_{19}NO_3SNa^+$ $[M+Na]^+$: 328.0978; found 328.0982. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 4:96, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 37.0 min, t_r(major) = 34.8 min.

*Methyl 3-((benzyloxy)amino)-2-(pyridin-4-ylmethyl) propanoate (**5e**)*

Light yellow oil: 29.7 mg, 99%; *ee* = 93% via (*E*)-**4e**; $[\alpha]_D^{20} = -6.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, J = 5.5 Hz, 2H), 7.36–7.26 (m, 5H), 7.07 (dd, J = 4.6, 1.3 Hz, 2H), 5.71 (s, 1H), 4.65 (d, J = 1.5 Hz, 2H), 3.59 (s, 3H), 3.18–2.81 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 150.0, 148.1, 137.7, 128.7, 128.6, 128.1, 124.5, 124.4, 76.6, 53.5, 52.2, 45.0, 35.6 ppm; HR-MS (ESI): m/z calcd. for $C_{17}H_{21}N_2O_3^+$ $[M+H]^+$: 301.1547; found 301.1553. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 20:80, UV 220 nm, flow rate 1.0 mL min^{-1}): t_r(minor) = 16.8 min, t_r(major) = 12.2 min.

*Methyl 3-((benzyloxy)amino)-2-(cyclopropylmethyl) propanoate (**5f**)*

Light yellow oil: 26.1 mg, 99%; *ee* = 99%; $[\alpha]_D^{20} = -13.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H), 5.71 (brs, 1H), 4.69 (d, J = 1.2 Hz, 2H), 3.68 (s, 3H), 3.15 (ddd, J = 17.6, 13.0, 6.9 Hz, 2H), 2.95–2.83 (m, 1H), 1.50 (t, J = 7.0 Hz, 2H), 0.77–0.61 (m, 1H), 0.51–0.42 (m, 2H), 0.09–0.02 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 137.9, 128.6, 128.5, 128.0, 76.5, 53.9, 51.9, 44.6, 35.7, 9.3, 4.9 ppm; HR-MS (ESI): m/z calcd. for $C_{15}H_{22}NO_3^+$ $[M+H]^+$: 264.1594; found 264.1589. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 4:96, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 26.4 min, t_r(major) = 23.6 min.

*Methyl 3-((benzyloxy)amino)-2-(cyclopentylmethyl) propanoate (**5g**)*

Light yellow oil: 28.8 mg, 99%; *ee* = 98%; $[\alpha]_D^{20} = -6.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 5H), 5.67 (brs, 1H), 4.65 (d, J = 1.2 Hz, 2H), 3.64 (s, 3H), 3.06 (ddd, J = 17.4, 13.0, 6.9 Hz, 2H), 2.78 (ddd, J = 14.4, 9.3, 5.0 Hz, 1H), 1.78–1.43 (m, 9H), 1.13–0.98 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 138.0, 128.6, 128.5, 128.0, 76.5, 54.6, 51.8, 43.8, 38.5, 37.1, 33.2, 32.9, 25.4 ppm; HR-MS (ESI): m/z calcd. for $C_{17}H_{26}NO_3^+$ $[M+H]^+$: 292.1907; found 292.1904. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 4:96, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 24.2 min, t_r(major) = 21.6 min.

*Methyl 3-((benzyloxy)amino)-2-(cyclohexylmethyl) propanoate (**5h**)*

Light yellow oil: 30.2 mg, 99%; *ee* = 96%; $[\alpha]_D^{20} = -9.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5H), 5.67 (brs, 1H), 4.66 (d, J = 1.3 Hz, 2H), 3.65 (s, 3H), 3.04 (ddd, J = 17.3, 12.9, 6.8 Hz, 2H), 2.91–2.79 (m, 1H), 1.77–1.55 (m, 6H), 1.32–1.15 (m, 5H), 0.92–0.80 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 137.9, 128.7, 128.5, 128.0, 76.6, 54.7, 51.9, 41.7, 38.4, 35.8, 33.8, 33.3, 26.9, 26.6 ppm; HR-MS (ESI): m/z calcd. for $C_{18}H_{28}NO_3^+$ $[M+H]^+$: 306.2064; found 306.2060. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane; = 4:96, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 22.7 min, t_r(major) = 19.8 min.

*Methyl 3-((benzyloxy)amino)-2-((1-benzylpiperidin-4-yl)methyl) propanoate (**5i**)*

Light yellow oil: 39.3 mg, 99%; *ee* = 98% via (*E*)-**4i**, *ee* = 97% via (*Z*)-**4i**; $[\alpha]_D^{20} = -4.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 10H), 5.65 (brs, 1H), 4.64 (d, J = 1.0 Hz, 2H), 3.64 (s, 3H), 3.46 (s, 2H), 3.03 (ddd, J = 17.5, 13.0, 6.8 Hz, 2H), 2.89–2.79 (m, 3H), 1.91 (td, J = 11.2, 2.8 Hz, 2H), 1.75–1.67 (m, 1H), 1.63–1.53 (m, 2H), 1.32–1.19 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 138.6, 137.9, 129.4, 128.6, 128.5, 128.3, 128.0, 127.1, 76.6, 63.7, 54.7, 54.0, 51.9, 41.8, 37.5, 34.1, 32.9, 32.3 ppm; HR-MS (ESI): m/z calcd. for $C_{24}H_{33}N_2O_3^+$ $[M+H]^+$: 397.2486; found 397.2479. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, *i*PrOH/*n*-hexane = 30:70, UV 220 nm, flow rate 0.3 mL min^{-1}): t_r(minor) = 27.0 min, t_r(major) = 20.4 min.

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