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Preparation of α,α-Disubstituted α-Amino Acid Derivatives via Alkyl Addition to α-Oxime Esters with Organozinc Species

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An α-oxime ester derivative prepared via treatment of an acetylenedicarboxylate or an α-keto ester with hydroxylamine underwent *C*-alkylation to the C=N bond of the oxime group by a Lewis-acid-promoted reaction with a trialkylzincate or a dialkylzinc reagent. The O–N bond of the thus obtained adduct was reductively cleaved under hydrogenolysis in the presence of the Pd-C catalyst to afford an α-amino ester. Treatment of the oxime derivative prepared from methyl 5-bromo-2-oxopentanoate with the trialkylzincate gave an α-alkyl proline derivative via the addition reaction followed by the intramolecular attack upon a bromine-bearing carbon. The reaction of ethyl 4-oxo-2-pentynoate with hydroxylamine formed an isoxazole derivative by way of the intramolecular attack of an in situ-generated oxime to the carbonyl group. From this isoxazole derivative, ethyl 2-amino-4-oxo-2-pentenoate was given by the Pd-C-catalyzed hydrogenolysis.

Introduction

α,α-Disubstituted α-amino acids, which are nonproteinogenic amino acids, are an interesting class of compounds[1] with regard to their biological properties[2] and the stable secondary structure of their peptides due to conformational restriction of the side chain.[3] A variety of methods for the preparation of these amino acids, which include bislactims,[4] oxazinones,[5] imidazolidinones,[6] nitrones,[7] dehydroamino acid derivatives,[8] 3-amino-2*H*-azirines,[9] the Strecker reaction of ketones,[10] and other procedures,[11] have been developed. Preparation of these intermediate materials has, however, often been troublesome. Although the nucleophilic *C*-alkylation of the C=N bond in α-imino esters with organometallic reagents might also be envisaged for the synthesis of disubstituted amino acids, few successful examples have been known due to the potential reactivity of organometallics with the ester functionality and the feasibility of *N*-alkylation[12] except with the use of alkylzinc bromide[13] or the imino compound substituted with a synthetic equivalent of a carboxylic group such as an orthoester[14] or C=C group.[15] The oxime group is very susceptible to *C*-alkylation via a radical pathway.[16] Thus, the α-oxime ester derivatives might also be envisaged as likely precursors of α,α-disubstituted α-amino acids. To the best of our knowledge, the oxime derivatives of α-keto esters, however, have only scrarcely been reported to undergo alkylation,[16c] while the oxime derivatives of glyoxylic acid which is a class of an α-aldehyde carboxylic acid reportedly bring about the formation of α-monosubstituted amino acid derivatives in the radical reaction[17] and in the reaction using allylzinc halides under aqueous conditions.[18]

We wish to present herein a novel method for preparation of α,α-disubstituted amino acid derivatives that was carried out by the reaction of α-oxime esters with alkylzinc reagents.

Results and Discussion

Initially, the alkyl addition to the C=N bond of the compound **1** was explored under various conditions. Preparation of **1** was achieved starting from dimethyl acetylenedicarboxylate **2**; that is, the reaction of **2** with hydroxylamine hydrochloride in methanol in the presence of sodium carbonate gave the oxime **3** in 83% yield. Then, treatment of **3** with NaH followed by benzyl bromide in DMF produced **1** in a quantitative yield (Scheme 1).

Glyoxylic oxime ether has been previously reported to undergo alkylation via a radical pathway in a system composed of alkyl iodide, Bu_3SnH, and Et_3B.[17] Thus, **1** was subjected to radical alkylation under similar conditions using isopropyl iodide as an alkyl iodide, resulting in no formation of the isopropylated product **4a**. The addition of $BF_3{\cdot}OEt_2$ as a Lewis acid to the reaction system brought about the production of **4a** in a trace amount (4.1% yield). Although a variety of reaction conditions (i.e., varying amounts of *i*PrI, Bu_3SnH, and Et_3B, reaction temperature,

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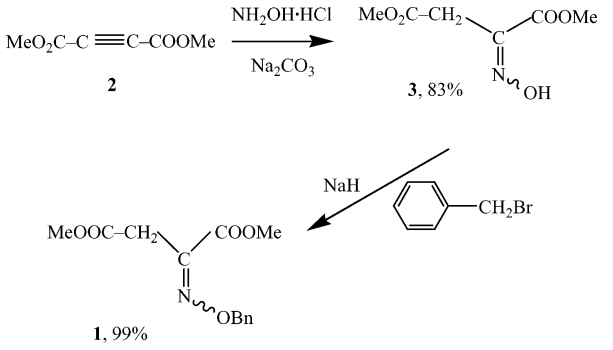
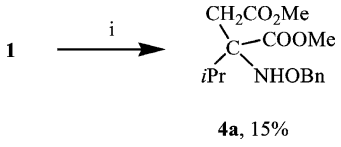


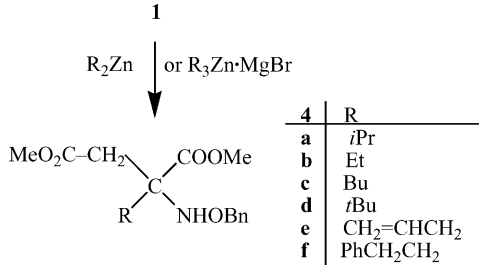
Scheme 1. Preparation of **1**.

a solvent, and a Lewis acid) were subsequently examined, the best result was found to be the formation of **4a** in only 15% yield (Scheme 2).



Scheme 2. Alkylation of **1** via radical pathway; i) *i*PrI (10 equiv.), Bu_3SnH (2.5 equiv.), Et_3B (2.5 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), $ClCH_2CH_2Cl$, reflux, 48 h.

The reaction of an α-imino ester with an alkylzinc bromide has been reported to proceed via regioselective *C*-alkylation of the imino group.[13] Thus, **1** was treated with [4-(ethoxycarbonyl)butyl]zinc bromide under different reaction temperatures (i.e., 0 °C, ambient temperature, or at reflux temperature in THF). Under these conditions, no addition product was formed along with low conversion of **1**. Addition of $BF_3{\cdot}OEt_2$ in order to enhance the electrophilicity of the oxime group of **1** gave no addition product. The addition reaction also did not proceed with the use of ethylzinc bromide instead of [4-(ethoxycarbonyl)butyl]zinc bromide (Scheme 3). Next, diethylzinc was subjected to a reaction with **1** in a CH_2Cl_2 solution, thus forming the ethyl addition product **4b** in 55% yield in the presence of $BF_3{\cdot}OEt_2$ (Table 1, run 1), although there was no formation of **4b** in the absence of $BF_3{\cdot}OEt_2$ (Table 1, run 2). The reaction at ambient temperature was very sluggish even in the presence of $BF_3{\cdot}OEt_2$ (Table 1, run 3). Use of solvents (i.e., Et_2O and THF) other than CH_2Cl_2 gave almost the same results as those obtained in a CH_2Cl_2 solution (Table 1, runs 4 and 5). The reactions in the presence of Lewis acids other than $BF_3{\cdot}OEt_2$ did not afford **4b** in better yields than that in the $BF_3{\cdot}OEt_2$-promoted reaction (Table 1, runs 6–8). Subsequently, the influence of amounts of $BF_3{\cdot}OEt_2$ upon the formation of **4b** was examined to reveal that enlargement or diminution from the equivalent amount lowered the yield of **4b** (Table 1, runs 9–11). An improvement of the yield of **4b** was achieved by increasing the amount of Et_2Zn to 2 equiv. (Table 1, run 12).



Scheme 3. Alkylation of **1** with a dialkylzinc or trialkylzincate reagent.

Next, in order to enhance the nucleophilicity of the organozinc species, the zincate complex, i.e., $Et_3Zn{\cdot}MgBr$, was subjected to a reaction with **1** in the presence of $BF_3{\cdot}OEt_2$. The reaction under reflux conditions diminished the yield of **4b** compared with that under the similar conditions using diethylzinc (Table 2, run 1). In contrast, the reaction at ambient temperature brought about the formation of **4b** in a modest yield, in contrast to diethylzinc (Table 2, run 2). At ambient temperature, **4b** was also formed without $BF_3{\cdot}OEt_2$ (Table 2, run 3). The yields of **4b** were increased by lowering the reaction temperature to 0 °C and increasing the amount of $Et_3Zn{\cdot}MgBr$ (Table 2, runs 4–6). The time-resolved analysis of the reaction revealed that 24 h were necessitated for almost all conversions of **1** (Table 2, runs 6–9). Use of $Ti(O\text{-}iPr)_4$ as a Lewis acid, however, afforded **4b** in a modest yield (65%) (Table 2, run 10).

Table 1. The reaction of **1** with diethylzinc.

Entry	Equiv. of Et_2Zn	Equiv. of Lewis acid	Solvent	Temp.	% Conversion	**4b** % Yield[a]
1	1	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	reflux	78	55
2	1	none	CH_2Cl_2	reflux	5	0
3	1	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	room temp.	8	3
4	1	$BF_3{\cdot}OEt_2$ (1)	Et_2O	reflux	70	51
5	1	$BF_3{\cdot}OEt_2$ (1)	THF	reflux	76	52
6	1	$Ti(O\text{-}iPr)_4$ (1)	CH_2Cl_2	reflux	97	40
7	1	$TiCl_4$ (1)	CH_2Cl_2	reflux	95	15
8	1	$SnCl_4$ (1)	CH_2Cl_2	reflux	97	11
9	1	$BF_3{\cdot}OEt_2$ (2)	CH_2Cl_2	reflux	18	11
10	1	$BF_3{\cdot}OEt_2$ (0.5)	CH_2Cl_2	reflux	66	49
11	1	$BF_3{\cdot}OEt_2$ (0.05)	CH_2Cl_2	reflux	50	34
12	2	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	reflux	85	76

[a] Based on the starting **1**.

Table 2. The reaction of **1** with triethylzincate.[a]

Entry	Equiv. of Et_3Zn·MgBr	Lewis acid	Temp.	Time [h]	% Conversion	**4b** % Yield[b]
1	1	BF_3·OEt_2	reflux	24	82	29
2	1	BF_3·OEt_2	room temp.	24	90	49
3	1	None	room temp.	24	94	22
4	1	BF_3·OEt_2	0 °C	24	74	64
5	1.5	BF_3·OEt_2	0 °C	24	85	72
6	2	BF_3·OEt_2	0 °C	24	99	82
7	2	BF_3·OEt_2	0 °C	1	24	20
8	2	BF_3·OEt_2	0 °C	3	37	32
9	2	BF_3·OEt_2	0 °C	12	54	48
10	2	Ti(O-*i*Pr)$_4$	0 °C	24	100	65

[a] Solvent: CH_2Cl_2. [b] Based on the starting **1**.

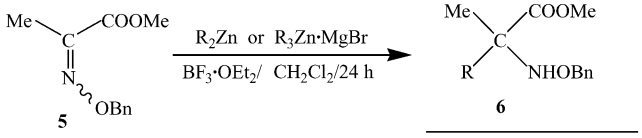
Trialkylzincates other than Et_3Zn·MgBr were subjected to a reaction with **1**. As a result, the products of type **4** based on alkyl addition to the oxime functionality were obtained in good yields, as shown in Table 3.

Table 3. The reaction of **1** with trialkylzincate.[a]

Entry	R_3Zn·MgBr R	Equiv.	% Conv.	Product **4**	% Yield[b]
1	*i*Pr	1	60	**a**	51
2	*i*Pr	2	69	**a**	67
3	Bu	2	82	**c**	72
4	*t*Bu	2	83	**d**	68
5	CH_2=$CHCH_2$	2	91	**e**	71
6	$PhCH_2CH_2$	2	68	**f**	50
7	$PhCH_2CH_2$	4	95	**f**	70

[a] Reaction conditions: CH_2Cl_2 solution, BF_3·OEt_2 (1 equiv.), 0 °C, 24 h. [b] Based on the starting **1**.

Next, the oxime ether derivative of methyl pyruvate, **5**, which was prepared via the reaction of methyl pyruvate with hydroxylamine followed by treatment with NaH/$PhCH_2Br$ was subjected to a reaction with alkylzincates. Ethyl- and butylzincates gave the *C*-alkylation products to the C=N bond, **6a**,**b** (Scheme 4), in good yields under the condition using 2 equiv. of the alkylzincates (Table 4, runs 1 and 2). While the isopropylzincate brought about a rather low yield of **6c** along with a sluggish conversion of **5** in the reaction using 2 equiv. of the zincate, use of 3 equiv. enhanced the conversion of **5** and improved the yield of **6c** (Table 4, runs 3 and 4). The allylzincate resulted in a lowered yield of **6d** in the reaction using 2 equiv. compared with that using 1 equiv. (Table 4, runs 5 and 6). The zinc reagent of the dialkyl type gave good results as with the addition of isopropyl and allyl groups (Table 4, runs 7 and 8).



6	R
a	Et
b	Bu
c	*i*Pr
d	CH_2=$CHCH_2$

Scheme 4. Alkylation of **5** with a dialkylzinc or trialkylzincate reagent.

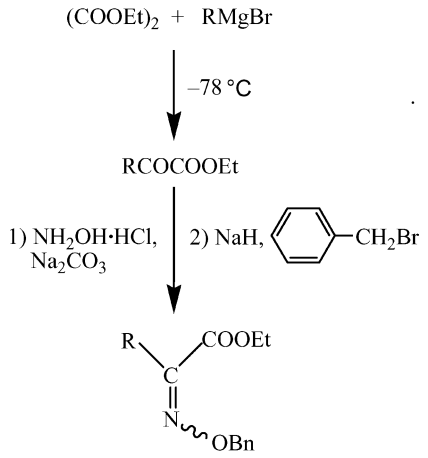
Table 4. The reaction of **5** with dialkylzinc or trialkylzincate.[a]

Entry	Alkylzinc reagent Type[b]	R	Equiv.	Temp.	% Conv.	Product **6**	% Yield[c]
1	A	Et	2	0 °C	100	**a**	85
2	A	Bu	2	0 °C	99	**b**	71
3	A	*i*Pr	2	0 °C	56	**c**	31
4	A	*i*Pr	3	0 °C	80	**c**	64
5	A	CH_2=$CHCH_2$	2	0 °C	100	**d**	23
6	A	CH_2=$CHCH_2$	1	0 °C	91	**d**	41
7	B	*i*Pr	2	reflux	78	**c**	66
8	B	CH_2=$CHCH_2$	2	reflux	100	**d**	68

[a] Reaction conditions: CH_2Cl_2 solution, BF_3·OEt_2 (1 equiv.), 24 h. [b] A = R_3Zn·MgBr, B = R_2Zn. [c] Based on the starting **5**.

Furthermore, α-oxime ester derivatives, **7a**,**b**, other than **1** or **5** were also subjected to a reaction with alkylzinc reagents. The preparation of **7a**,**b** was achieved by the reaction of diethyl oxalate with a Grignard reagent[19] followed by transformation to the oxime ether derivatives, as shown in Scheme 5. At first, **7a** was subjected to the reaction with 2 equiv. of Bu_3Zn·MgBr in a CH_2Cl_2 solution at 0 °C, which was the condition of choice for butylation of **5**. The conversion of **7a**, however, was low and was accompanied by no formation of the addition product, **8a**, (Table 5, run 1). The reaction was next performed under reflux conditions, resulting in modest improvement of the conversion of **7a** and the yield of **8a** (Table 5, run 2). Furthermore, the reaction temperature was raised to the reflux condition in a solution using 1,2-dichloroethane instead of CH_2Cl_2 as a solvent (Scheme 6). As a result, the yield of **8a** was rather diminished, although the conversion of **7a** progressed (Table 5, run 3). The increase in the amount of Bu_3Zn·MgBr to 4 equiv. afforded a modest yield (46%) of **8a** along with almost quantitative consumption of **7a** at ambient temperature, and a good yield (74%) of **8a** under reflux (Table 5, runs 4 and 5). In turn, the reactions of **7a** with the zincates composed of an alkyl group other than butyl were explored. Triethylzincate produced **8b** in a good yield at ambient temperature, while in a modest yield at reflux temperature (Table 5, runs 6 and 7). Triisopropylzincate also produced **8c** in a good yield at ambient temperature. In the reaction of triallylzincate, while use of 4 equiv. brought about the formation of **8d** in a modest yield, use of 2 equiv. afforded **8d** in a good yield (Table 5, runs 9 and

10). The reaction of **7b** with triallylzincate formed **8e** in a good yield under the condition using 2 equiv. of the zincate at ambient temperature.



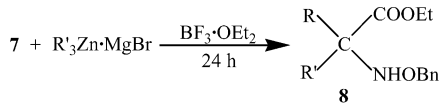
7	R	% Yield
a	Bu	83
b	*i*Pr	52

Scheme 5. Preparation of **7**.

Table 5. The reaction of **7** with trialkylzincate.[a]

Entry	7	R_3Zn·MgBr R	Equiv.	Solvent	Temp.	% Conv.	Product 8	% Yield[b]
1	**a**	Bu	2	CH_2Cl_2	0 °C	13	**a**	0
2	**a**	Bu	2	CH_2Cl_2	reflux	49	**a**	35
3	**a**	Bu	2	$ClCH_2CH_2Cl$	reflux	87	**a**	18
4	**a**	Bu	4	CH_2Cl_2	r.t.	92	**a**	46
5	**a**	Bu	4	CH_2Cl_2	reflux	99	**a**	74
6	**a**	Et	4	CH_2Cl_2	reflux	100	**b**	37
7	**a**	Et	4	CH_2Cl_2	r.t.	100	**b**	67
8	**a**	*i*Pr	4	CH_2Cl_2	r.t.	100	**c**	69
9	**a**	$CH_2=CHCH_2$	4	CH_2Cl_2	r.t.	100	**d**	47
10	**a**	$CH_2=CHCH_2$	2	CH_2Cl_2	r.t.	100	**d**	72
11	**b**	$CH_2=CHCH_2$	2	CH_2Cl_2	r.t.	100	**e**	66

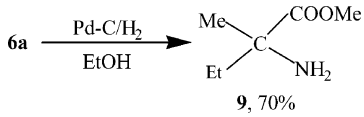
[a] Reaction conditions: BF_3·OEt_2 (1 equiv.), 24 h. [b] Based on the starting material **7**.



8	R	R'
a	Bu	Bu
b	Bu	Et
c	Bu	*i*Pr
d	Bu	$CH_2=CHCH_2$
e	*i*Pr	$CH_2=CHCH_2$

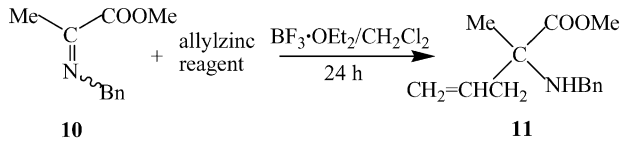
Scheme 6. Alkylation of **7** with trialkylzincate.

The reductive cleavage of the N–O bond, which is included in the addition product obtained by the above-mentioned reaction, to generate the NH_2 functionality is already known to be achieved by a variety of methods.[20] Actually, the Pd-C-catalyzed hydrogenolysis of **6a** at ambient pressure in an ethanol solution gave the α-amino ester, **9**, in good yield, as shown in Scheme 7.



Scheme 7. Pd-C catalyzed hydrogenolysis of **6a**.

The allyl addition reaction to the imine functionality was subsequently examined. The benzylimine derivative, **10**, of methyl pyruvate was used for this exploration. The result was that the reaction with $(allyl)_3Zn$·MgBr, $(allyl)_2Zn$, or allylZnCl in the presence of BF_3·OEt_2 at 0 °C afforded the allylation product, **11**, in low yields, while **10** was entirely consumed, as shown in Scheme 8. Lowering the reaction temperature to –10 °C did not bring about an improvement in the yield of **11**.

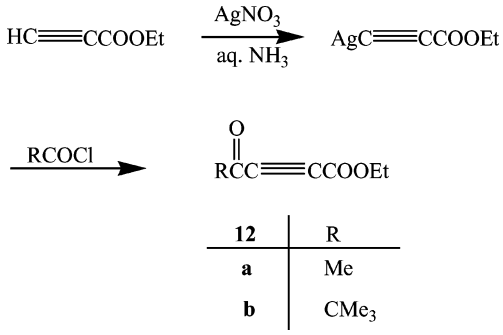


Allylzinc reagent	Temp.	% Yield
$(allyl)_3Zn$·MgBr	0 °C	19
$(allyl)_2Zn$	0 °C	9
allylZnCl	0 °C	10
$(allyl)_3Zn$·MgBr	–10 °C	8

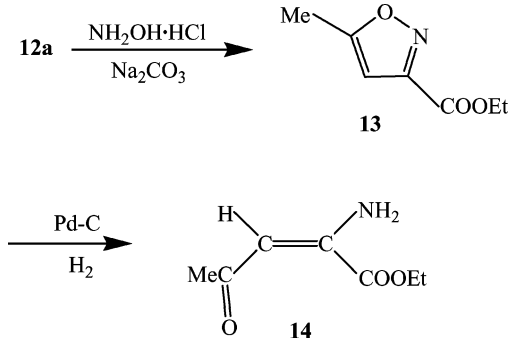
Scheme 8. The reaction of α-imino ester **10** with allylzinc reagent.

The next target was aimed at the synthesis of α-amino acid derivatives bearing a keto group. The keto-ynoates **12a**,**b** as the precursors of the oxime esters were prepared according to the procedure shown in Scheme 9.[21] Similar to the preparation of **1** from **2**, **12a** was subjected to treatment with hydroxylamine. The expected α-oxime ester derivative, however, was not formed, but the isoxazole derivative **13**, which is likely produced by way of the intramolecular attack of the initially formed oxime at the carbonyl group, was obtained in 81% yield. Treatment of **13** with the triethylzincate in the presence of BF_3·OEt_2 resulted only in recovery of **13**. In contrast, the subjection of **13** to Pd-C-catalyzed hydrogenolysis at ambient pressure in a EtOH solution gave the γ-keto vinylogous α-amino ester **14** in 76% yield (Scheme 10). Next, envisaging the formation of the γ-keto α-oxime ester derivative, *O*-benzylhydroxylamine was subjected to the reaction with **12a**. As a result, a mixture of the α- and β-oxime esters, which were assigned by the observation of peaks for $EtOOCC{=}NOBn^+$ and $CH_3COC{=}NOBn^+$, respectively, in the GC-MS spectra, was obtained. In order to suppress the formation of the β-isomer, **12b** bearing the bulky keto group was treated with *O*-benzylhydroxylamine to selectively give the α-oxime ester derivative **15** (Scheme 11). The reaction of **15** with the triethylzincate or diethylzinc species in the presence of

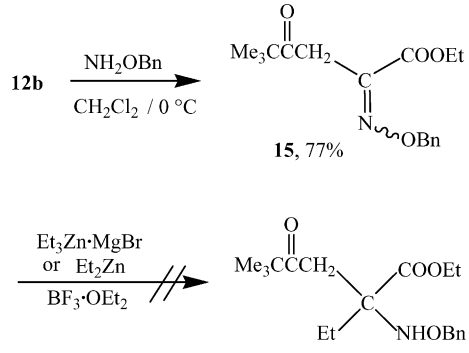
BF_3·OEt_2 did not afford the addition product to the C=N bond, although **15** was entirely consumed. The volatile product was not detected by GC analysis of the reaction mixture, and TLC analysis revealed it to be composed of a complex mixture. Thus, nonvolatile products based on the reaction of the aldol type will likely be formed due to the higher acidity of the methylene group of **15** compared with that of **1**.



Scheme 9. Preparation of γ-ketoynoates **12**.

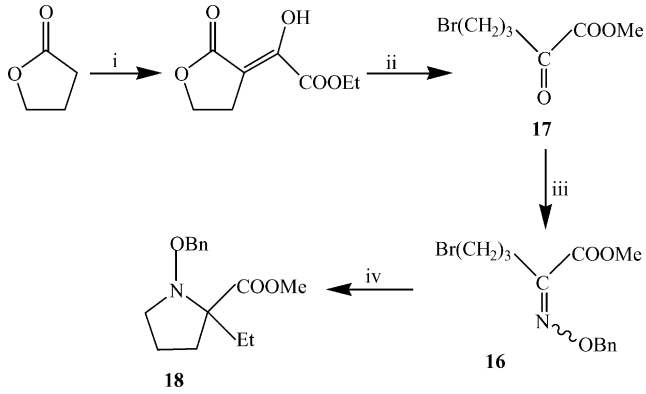


Scheme 10. Synthesis of a γ-keto α,β-unsaturated α-amino acid derivative from **12a**.



Scheme 11. Preparation of γ-keto α-oxime ester derivative **15** and its reaction with a triethylzincate or diethylzinc reagent.

The α-oxime ester derivative, **16**, bearing a bromine functionality was explored as the next substrate. The preparation of **16** was achieved by treatment of 5-bromo-2-oxopentanoate **17**, which was synthesized from γ-butyrolactone according to a literature procedure,[22] with *O*-benzylhydroxylamine. The reaction of **16** with triethylzincate in the presence of BF_3·OEt_2 afforded the cyclic α-substituted proline derivative **18**, which is considered to be formed via addition of the ethyl group to the C=N bond, followed by the intramolecular attack upon a bromine-bearing carbon, in 77% yield, as shown in Scheme 12.



Scheme 12. Synthesis of a proline derivative **18**; i) $(COOEt)_2$, NaOEt/EtOH; ii) 1) HBr/AcOH, 2) H_2SO_4/MeOH; iii) NH_2OBn/MeOH; iv) Et_3Zn·MgBr, BF_3·OEt_2, CH_2Cl_2, 0 °C, 24 h.

Conclusions

In this investigation, we have developed a novel procedure for the synthesis of α,α-disubstituted amino acid derivatives that involves a Lewis-acid-promoted reaction of ester derivatives bearing an oxime ether functionality at the α-position with trialkylzincates or dialkylzinc reagents. 5-Bromine-2-oxime ester derivatives lead to a proline derivative via an intramolecular substitution reaction following an addition reaction to the oxime group.

Experimental Section

General: ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a JNM GX400 spectrometer for $CDCl_3$ solution; chemical shifts (δ) are given in ppm relative to Me_4Si (internal standard); coupling constants (J) are given in Hz. Mass spectra were recorded with a Hitachi M-80B instrument. Column chromatography was performed with SiO_2 (Wako gel C-300HG, particle size 0.04–0.06 mm).

Preparation of Dimethyl 2-(Benzyloxyimino)succinate (1): To a MeOH solution (30 mL) of dimethyl acetylenedicarboxylate (2.137 g, 15 mmol), an aqueous solution (8 mL) of hydroxylammonium chloride (1.255 g, 18 mmol) was added. An aqueous solution (10 mL) of sodium carbonate (0.954 g, 9 mmol) was added at 0 °C to the resulting solution. After stirring for 1.5 h at 0 °C, MeOH was mostly removed under reduced pressure and the residue was extracted with $CHCl_3$. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. To the residue, hexane (15 mL) was added to crystallize **3** (2.205 g, 84%). ^{1}H NMR: δ = 3.71 (s, 5 H, CH_2COOCH_3), 3.88 (s, 3 H, $COOCH_3$), 10.48 (s, 1 H, NOH) ppm. MS (EI): *m*/*z* (%) = 175 (1) [M^+], 143 (79), 59 (100).

To a DMF suspension (20 mL) of NaH (0.120 g, 5 mmol), a DMF solution (4 mL) of benzyl bromide (0.855 g, 5 mmol) and a DMF solution (6 mL) of **3** (0.875 g, 5 mmol) were successively added at

0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 8 h at 0 °C. After the solvent was mostly removed under reduced pressure, H_2O (10 mL) was added to the residue and the product was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent: CH_2Cl_2/hexane, 1:1) to afford **1** (1.219 g, 92%) as a colorless oil. ^{1}H NMR: δ = 3.63 (s, 3 H, CH_2COOCH_3), 3.66 (s, 2 H, CH_2COOCH_3), 3.87 (s, 3 H, $COOCH_3$), 5.33 (s, CH_2Ph), 7.34 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 31.4, 52.3, 53.1, 78.2, 128.1, 128.3, 128.8, 135.9, 145.5, 163.1, 168.1 ppm. HRMS (EI): calcd. for $C_{13}H_{15}NO_5$ [M^+] 265.0949; found 265.0932.

Methyl 3-(Benzyloxyamino)-3-(methoxycarbonyl)-4-methylpentanoate (4a): To a CH_2Cl_2 solution (10 mL) of **1** (0.265 g, 1 mmol), $BF_3{\cdot}OEt_2$ (0.142 g, 1 mmol) was added at 0 °C under a nitrogen atmosphere and the solution was stirred for 10 min. To this was added a triisopropylzincate solution that was generated via stirring for 1 h after the addition of isopropylmagnesium bromide (1 mmol/1 mL, 6 mL) to a CH_2Cl_2 solution (4 mL) of $ZnCl_2$ (0.273 g, 2 mmol) in another flask. After stirring for 24 h at 0 °C, saturated aqueous ammonium chloride was added to the reaction mixture. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$. After the solvent was mostly removed under reduced pressure, the residue was subjected to column chromatography on silica gel (eluent: CH_2Cl_2) to afford **4a** (0.207 g, 67%) as a colorless oil. ^{1}H NMR: δ = 0.92 (d, J = 7.2 Hz, 3 H, CHCH_3), 0.97 (d, J = 7.2 Hz, 3 H, CHCH_3), 2.17 [septett, J = 7.2 Hz, 1 H, $CH(CH_3)_2$], 2.88 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 2.99 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 3.62 (s, 3 H, CH_2COOCH_3), 3.76 (s, 3 H, $COOCH_3$), 4.70 (s, 2 H, CH_2Ph), 6.47 (s, 1 H, NH), 7.32 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 17.4, 17.8, 32.9, 36.7, 51.7, 52.1, 69.8, 79.0, 127.6, 128.1, 128.2, 137.3, 171.7, 172.4 ppm. HRMS (EI): calcd. for $C_{16}H_{23}NO_5$ [M^+] 309.1574; found 309.1556.

Methyl 3-(Benzyloxyamino)-3-(methoxycarbonyl)pentanoate (4b): Using the procedure described for the formation of **4a**, **4b** was obtained as a colorless oil (0.242 g, 82%) by the reaction of **1** (1 mmol) with triethylzincate (2 mmol). ^{1}H NMR: δ = 0.88 (t, J = 8.0 Hz, 3 H, CH_2CH_3), 1.72–1.84 (m, 2 H, CH_2CH_3), 2.85 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 2.90 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 3.66 (s, 3 H, CH_2COOCH_3), 3.75 (s, 3 H, COOCH_3), 4.71 (s, 2 H, CH_2Ph), 6.72 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.2, 27.0, 36.9, 51.5, 52.1, 67.4, 78.8, 127.5, 127.9, 128.2, 137.2, 170.9, 172.8 ppm. HRMS (EI): calcd. for $C_{15}H_{21}NO_5$ [M^+] 295.1418; found 295.1412.

Methyl 3-(Benzyloxyamino)-3-(methoxycarbonyl)heptanoate (4c): Using the procedure described for the formation of **4a**, **4c** was obtained as a colorless oil (0.233 g, 72%.) by the reaction of **1** (1 mmol) with tributylzincate (2 mmol). ^{1}H NMR: δ = 0.89 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.25–2.00 (m, 6 H, $CH_2CH_2CH_2CH_3$), 2.85 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 2.92 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 3.66 (s, 3 H, CH_2COOCH_3), 3.75 (s, 3 H, COOCH_3), 4.71 (s, 2 H, CH_2Ph), 6.30 (s, 1 H, NH), 7.35 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 13.8, 19.2, 30.7, 31.0, 31.5, 51.7, 52.3, 66.1, 78.1, 127.8, 128.2, 128.4, 137.2, 168.4, 171.4 ppm. HRMS (EI): calcd. for $C_{17}H_{25}NO_5$ [M^+] 323.1731; found 323.1701.

Methyl 3-(Benzyloxyamino)-4,4-dimethyl-3-(methoxycarbonyl)pentanoate (4d): Using the procedure described for the formation of **4a**, **4d** was obtained as a colorless oil (0.220 g, 68%) by the reaction of 1 (1 mmol) with tri-*tert*-butylzincate (2 mmol). ^{1}H NMR: δ = 0.98 [s, 9 H, $C(CH_3)_3$], 2.85 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 3.00 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 3.55 (s, 3 H, CH_2COOCH_3), 3.77 (s, 3 H, $COOCH_3$), 4.62 (d, J = 12.0 Hz, 1 H, CHPh), 4.69 (d, J = 12.0 Hz, 1 H, CHPh), 6.52 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 26.5, 34.6, 37.3, 51.6, 52.0, 71.5, 76.1, 127.5, 128.1, 128.9, 137.2, 171.1, 172.8 ppm. HRMS (EI): calcd. for $C_{17}H_{25}NO_5$ [M^+] 323.1731; found 323.1746.

Methyl 3-(Benzyloxyamino)-3-(methoxycarbonyl)-5-hexenoate (4e): Using the procedure described for the formation of **4a**, **4e** was obtained as a colorless oil (0.189 g, 71%) by the reaction of **1** (1 mmol) with triallylzincate (2 mmol). ^{1}H NMR: δ = 2.48–2.61 (m, 2 H, $CH_2CH{=}CH_2$), 2.83 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 2.88 (d, J = 16.0 Hz, 1 H, CHCOOCH$_3$), 3.66 (s, 3 H, CH_2COOCH_3), 3.75 (s, 3 H, $COOCH_3$), 4.72 (s, 2 H, CH_2Ph), 5.10–5.15 (m, 2 H, $CH_2{=}$CH), 5.68–5.78 (m, 1 H, $CH_2{=}CHCH_2$), 6.26 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 37.3, 38.3, 51.7, 52.3, 67.0, 76.8, 119.5, 127.6, 128.1, 128.2, 131.5, 137.2, 170.8, 172.4 ppm. HRMS (EI): calcd. for $C_{13}H_{16}NO_5$ [M^+] 266.1027; found 266.1001.

Methyl 3-(Benzyloxyamino)-3-(methoxycarbonyl)-5-phenylpentanoate (4f): Using the procedure described for the formation of **4a**, **4f** was obtained as a colorless oil (0.260 g, 70%) by the reaction of **1** (1 mmol) with tris(2-phenylethyl)zincate generated via the addition of 2-phenylethylmagnesium bromide (1 mmol/1 mL, 12 mL) to a CH_2C_2 solution (8 mL) of $ZnCl_2$ (0.545 g, 4 mmol). ^{1}H NMR: δ = 1.96–2.15 (m, 2 H, CH_2CH_2Ph), 2.54–2.71 (m, 2 H, CH_2CH_2Ph), 2.93 (s, 2 H, CH_2COOCH$_3$), 3.67 (s, 3 H, CH_2COOCH_3), 3.75 (s, 3 H, $COOCH_3$), 4.76 (s, 2 H, OCH_2Ph), 6.31 (s, 1 H, NH), 7.20 (br. s, 5 H, Ph), 7.34 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 30.0, 35.8, 37.4, 51.5, 52.2, 66.8, 77.1, 125.7, 127.5, 128.00, 128.02, 128.1, 128.2, 137.1, 140.8, 170.8, 172.7 ppm. MS (EI): m/z (%) = 312 (18) [M – $COOCH_3$]$^+$, 91 (100). MS (CI): m/z = 372 [M + 1]$^+$. HRMS (EI): calcd. for $C_{19}H_{22}NO_3$ [M – $COOCH_3$]$^+$ 312.1598; found 312.1610.

Methyl 2-(Benzyloxyimino)propionate (5): Using the procedure described for the formation of **1**, **5** was obtained as a colorless oil (77%) via the reaction of methyl pyruvate. ^{1}H NMR: δ = 2.05 (s, 3 H, $CH_3C{=}N$), 3.85 (s, 3 H, $COOCH_3$), 5.31 (s, 2 H, CH_2Ph), 7.35 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 11.8, 52.8, 77.6, 128.1, 128.2, 128.3, 136.4, 149.1, 164.0 ppm. MS (EI): m/z (%) = 207 (1) [M^+], 176 (10), 91 (100).

Methyl 2-(Benzyloxyamino)-2-methylbutanoate (6a): Using the procedure described for the formation of **4a**, **6a** was obtained as a colorless oil (0.201 g, 85%) by the reaction of **5** (0.207 g, 1 mmol) with triethylzincate (2 mmol). ^{1}H NMR: δ = 0.86 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 1.33 (s, 3 H, $CH_3CCOOCH_3$), 1.60 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.72 (s, 3 H, $COOCH_3$), 4.68 (d, J = 12.0 Hz, 1 H, CHPh), 4.75 (d, J = 12.0 Hz, 1 H, CHPh), 6.02 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 8.2, 19.1, 28.8, 52.1, 66.1, 76.9, 127.5, 128.1, 128.4, 137.6, 175.4 ppm. HRMS (EI): calcd. for $C_{13}H_{19}NO_3$ [M^+] 237.1364; found 237.1387.

Methyl 2-(Benzyloxyamino)-2-methylhexanoate (6b): Using the procedure described for the formation of **6a**, **6b** was obtained as a colorless oil (0.188 g, 71%) by the reaction of **5** (1 mmol) with tributylzincate (2 mmol). ^{1}H NMR: δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.25–1.30 (m, 4 H, $CH_3CH_2CH_2$), 1.35 (s, 3 H, $CH_3CCOOCH_3$), 1.51–1.55 (m, 2 H, $CH_3CH_2CH_2CH_2$), 4.67 (d, J = 11.8 Hz, 1 H, CHPh), 4.73 (d, J = 11.8 Hz, 1 H, CHPh), 6.01 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 13.9, 19.4, 23.0, 25.7, 35.7, 51.9, 65.6, 76.8, 127.4, 127.9, 128.2, 137.5, 175.3 ppm. HRMS (EI): calcd. for $C_{15}H_{23}NO_3$ [M^+] 265.1677; found 265.1692.

Methyl 2-(Benzyloxyamino)-2,3-dimethylbutanoate (6c): To a CH_2Cl_2 solution (10 mL) of **5** (1 mmol), $BF_3{\cdot}OEt_2$ (1 mmol) was

added at 0 °C under a nitrogen atmosphere and the solution was stirred for 10 min. To this was added a bis(isopropyl)zinc solution that was generated via stirring for 1 h after the addition of isopropylmagnesium bromide (1 mmol/1 mL, 4 mL) to a CH_2Cl_2 solution (4 mL) of $ZnCl_2$ (2 mmol) in another flask. After stirring for 24 h under reflux, the reaction mixture was worked up according to the procedure described for the formation of **4a** to afford **6c** (0.166 g, 66%) as a colorless oil. ^{1}H NMR: δ = 0.82 (d, J = 7.0 Hz, 3 H, CHCH_3), 0.90 (d, J = 7.0 Hz, 3 H, CHCH_3), 1.28 (s, 3 H, CH_3CCOOCH$_3$), 1.80 [septett, J = 7.0 Hz, 1 H, CH(CH$_3$)$_2$], 3.72 (s, 3 H, COOCH_3), 4.64 (d, J = 11.6 Hz, 1 H, CHPh), 4.72 (d, J = 11.6 Hz, 1 H, CHPh), 6.03 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.7, 17.2, 17.6, 33.4, 51.9, 69.1, 77.2, 127.5, 128.1, 128.3, 137.7, 157.7 ppm. HRMS (EI): calcd. for $C_{14}H_{21}NO_4$ [M$^+$] 251.1520; found 251.1540.

Methyl 2-(Benzyloxyamino)-2-methyl-4-pentenoate (6d): Using the procedure described for the formation of **6c**, **6d** was obtained as a colorless oil (0.169 g, 68%) by the reaction of **5** (1 mmol) with diallylzinc (2 mmol). ^{1}H NMR: δ = 1.31 (s, 3 H, CH_3CCOOCH$_3$), 2.33–2.45 (m, 2 H, CH_2CH=CH$_2$), 3.72 (s, 3 H, COOCH$_3$), 4.71 (s, 2 H, CH_2Ph), 5.07–5.12 (m, 2 H, CH_2=CH), 5.69–5.79 (m, 1 H, CH$_2$=CH), 6.02 (s, 1 H, NH), 7.34 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 19.6, 39.9, 51.9, 65.2, 76.8, 118.6, 127.4, 127.9, 132.1, 137.4, 137.9, 174.6 ppm. HRMS (EI): calcd. for $C_{14}H_{19}NO_3$ [M$^+$] 249.1364; found 249.1351.

Ethyl 2-(Benzyloxyimino)hexanoate (7a): Ethyl 2-oxohexanoate was produced according to the published procedure[19] (96%) and then subjected to the procedure described for the formation of **1** to afford **7a** as a colorless oil (83%). ^{1}H NMR: δ = 0.88 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$CH$_2$CH$_2$), 1.29–1.36 (m, 5 H, CH$_3$$CH_2CH_2CH_2$, CH_3CH$_2$O), 1.48 (quint, J = 7.6 Hz, 2 H, CH$_3$CH$_2$$CH_2CH_2$), 2.59 (t, J = 7.6 Hz, 2 H, CH$_3$CH$_2$CH$_2$$CH_2$), 4.31 (q, J = 7.0 Hz, 2 H, CH$_3$$CH_2$O), 5.28 (s, 2 H, CH$_2$Ph), 7.35 (br. s, 5 H, Ph) ppm. ^{13}CNMR: δ = 13.7, 14.1, 22.6, 25.4, 28.1, 61.5, 77.2, 127.7, 127.9, 128.1, 136.5, 153.1, 163.3 ppm. MS (EI): m/z (%) = 263 (1) [M$^+$], 220 (10), 91 (100).

Ethyl 2-(Benzyloxyimino)-3-methylbutanoate (7b): Ethyl 3-methyl-2-oxobutanoate was produced according to the literature procedure[19] (77%) and then subjected to the procedure described for the formation of **1** to afford **7b** as a colorless oil (52%). ^{1}H NMR: δ = 1.18 [d, J = 7.2 Hz, 6 H, CH(CH_3)$_2$], 1.31 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$O), 2.68 [septett, J = 7.2 Hz, 1 H, CH(CH$_3$)$_2$], 4.26 (q, J = 7.2 Hz, 2 H, CH$_3$$CH_2$O), 5.22 (s, 2 H, CH$_2$Ph), 7.32 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.1, 14.2, 30.9, 61.1, 77.0, 127.7, 127.9, 128.2, 137.3, 156.7, 163.6 ppm. MS (EI): m/z (%) = 249 (1) [M$^+$], 204 (10), 91 (100).

Ethyl 2-(Benzyloxyamino)-2-butylhexanoate (8a): To a CH_2Cl_2 solution (10 mL) of **7a** (0.263 g, 1 mmol), BF_3·OEt_2 (1 mmol) was added at 0 °C under a nitrogen atmosphere. After stirring for 10 min, to the resulting solution was added a tributylzincate solution that was generated via stirring for 1 h after the addition of butylmagnesium bromide (1 mmol/1 mL, 12 mL) to a CH_2Cl_2 solution (8 mL) of $ZnCl_2$ (4 mmol) in another flask. After stirring for 24 h under reflux, the reaction mixture was worked up according to the procedure described for the formation of **4a** to afford **8a** (0.238 g, 74%) as a colorless oil. ^{1}H NMR: δ = 0.90 (t, J = 7.0 Hz, 6 H, CH_3CH$_2$CH$_2$), 1.18–1.36 (m, 11 H, COOCH$_2$$CH_3$, CH$_3$$CH_2$$CH_2$), 1.62–1.71 (m, 4 H, CH$_3CH_2CH_2$$CH_2$), 4.18 (q, J = 7.2 Hz, 2 H, COOCH_2CH$_3$), 4.69 (s, 2 H, CH_2Ph), 5.90 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.0, 14.3, 23.0, 25.4, 31.6, 60.5, 68.2, 76.3, 127.3, 127.8, 127.9, 137.7, 174.3 ppm. HRMS (EI): calcd. for $C_{19}H_{31}NO_3$ [M$^+$] 321.2302; found 321.2272.

Ethyl 2-(Benzyloxyamino)-2-ethylhexanoate (8b): To a CH_2Cl_2 solution (10 mL) of **7a** (1 mmol), BF_3·OEt_2 (1 mmol) was added at 0 °C under a nitrogen atmosphere and the solution was stirred for 10 min To this was added a triethylzincate solution that was generated via stirring for 1 h after the addition of ethylmagnesium bromide (1 mmol/1 mL, 12 mL) to a CH_2Cl_2 solution (8 mL) of $ZnCl_2$ (4 mmol) in another flask. After stirring for 24 h at ambient temperature, the reaction mixture was worked up according to the procedure described for the formation of **4a** to afford **8b** (0.196 g, 67%) as a colorless oil. ^{1}H NMR: δ = 0.86 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$CH$_2$), 0.90 (t, J = 6.8 Hz, 3 H, CH_3CH$_2$CCOOCH$_2$), 1.20–1.33 (m, 7 H, COOCH$_2$$CH_3$, CH$_3$$CH_2$$CH_2$), 1.59–1.78 (m, 4 H, CH$_3CH_2CH_2$$CH_2$, CH$_3$$CH_2$CCOOCH$_2$), 4.19 (q, J = 7.0 Hz, COOCH_2CH$_3$), 5.11 (s, 2 H, CH_2Ph), 6.05 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 7.7, 14.0, 14.3, 23.0, 24.6, 25.4, 31.3, 60.6, 68.6, 76.3, 127.3, 127.7, 127.9, 137.5, 174.1 ppm. HRMS (EI): calcd. for $C_{17}H_{27}NO_3$ [M$^+$] 293.1989; found 293.1987.

Ethyl 2-(Benzyloxyamino)-2-isopropylhexanoate (8c): Using the procedure described for the formation of **8b**, **8c** was obtained as a colorless oil (0.213 g, 69%) by the reaction of **7a** (1 mmol) with triisopropylzincate (4 mmol). ^{1}H NMR: δ = 0.90–0.96 [m, 9 H, CH_3CH$_2$CH$_2$, CH(CH_3)$_2$], 1.28 (t, J = 7.0 Hz, 3 H, COOCH$_2$$CH_3$), 1.31–1.43 (m, 4 H, CH$_3$$CH_2$$CH_2$), 1.84 (t, J = 7.8 Hz, 2 H, CH$_3$CH$_2$CH$_2$$CH_2$), 2.03–2.13 [m, 1 H, CH(CH$_3$)$_2$], 4.18 (q, J = 7.0 Hz, 2 H, COOCH_2CH$_3$), 4.69 (d, J = 11.6 Hz, 1 H, CHPh), 4.73 (d, J = 11.6 Hz, 1 H, CHPh), 6.14 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.2, 14.4, 17.4, 18.1, 23.4, 26.2, 31.2, 31.9, 60.5, 70.9, 79.2, 127.4, 127.9, 128.1, 137.8, 173.2 ppm. MS (EI): m/z (%) = 264 (40) [M – iPr]$^+$, 91 (100). MS (CI): m/z = 308 [M + 1]$^+$. HRMS (EI): calcd. for $C_{15}H_{22}NO_3$ [M – iPr]$^+$ 264.1598; found 264.1573.

Ethyl 2-(Benzyloxyamino)-2-(2-propenyl)hexanoate (8d): To a CH_2Cl_2 solution (10 mL) of **7a** (1 mmol), BF_3·OEt_2 (1 mmol) was added at 0 °C under a nitrogen atmosphere and the solution was stirred for 10 min. To this was added a triallylzincate solution that was generated via stirring for 1 h after the addition of allylmagnesium bromide (1 mmol/1 mL, 6 mL) to a CH_2Cl_2 solution (4 mL) of $ZnCl_2$ (2 mmol) in another flask. After stirring for 24 h at ambient temperature, the reaction mixture was worked up according to the procedure described for the formation of **4a** to afford **8d** (0.220 g, 72%) as a colorless oil. ^{1}H NMR: δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$CH$_2$), 1.20–1.29 (m, 7 H, COOCH$_2$$CH_3$, CH$_3$$CH_2$$CH_2$), 1.55–1.64 (m, 2 H, CH$_3CH_2CH_2$$CH_2$), 2.45–2.61 (m, 2 H, CH_2CH=CH$_2$), 4.19 (q, J = 7.2 Hz, 2 H, COOCH_2CH$_3$), 4.70 (d, J = 12.0 Hz, 1 H, CHPh), 4.73 (d, J = 12.0 Hz, 1 H, CHPh), 5.09–5.14 (m, 2 H, CH_2=CH), 5.74–5.85 (m, 1 H, CH$_2$=CHCH$_2$), 5.92 (s, 1 H, NH), 7.33 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 13.9, 14.3, 22.9, 25.4, 32.2, 36.2, 60.7, 68.0, 76.3, 118.1, 127.3, 127.7, 128.0, 132.7, 137.5, 173.6 ppm. MS (EI): m/z (%) = 264 (20) [M – CH$_2$CH=CH$_2$]$^+$, 91 (100). MS (CI): m/z = 306 [M + 1]$^+$. HRMS (EI): calcd. for $C_{15}H_{22}NO_3$ [M – CH$_2$CH=CH$_2$]$^+$ 264.1598; found 264.1592.

Ethyl 2-(Benzyloxyamino)-2-isopropyl-4-pentenoate (8e): Using the procedure described for the formation of **8d**, **8e** was obtained as a colorless oil (0.192 g, 66%) by the reaction of **7b** (0.249 g, 1 mmol) with triallylzincate (2 mmol). A colorless oil. ^{1}H NMR: δ = 0.93 (d, J = 7.2 Hz, 3 H, CHCH_3), 0.95 (d, J = 7.2 Hz, 3 H, CHCH_3), 1.27 (t, J = 7.2 Hz, 3 H, COOCH$_2$$CH_3$), 1.97–2.07 [m, 1 H, CH(CH$_3$)$_2$], 2.61–2.74 (m, 2 H, CH_2CH=CH$_2$), 4.19 (q, J = 7.2 Hz, 2 H, COOCH_2CH$_3$), 4.69 (d, J = 11.6 Hz, 1 H, CHPh), 4.74 (d, J = 11.6 Hz, 1 H, CHPh), 5.05–5.16 (m, 2 H, CH_2=CH), 5.86–5.96 (m, 1 H, CH$_2$=CHCH$_2$), 6.13 (s, 1 H, NH), 7.32 (br. s, 5 H, Ph)

ppm. ^{13}C NMR: δ = 14.3, 17.1, 17.8, 31.8, 35.3, 60.5, 70.7, 76.1, 117.4, 127.3, 127.8, 127.9, 134.1, 137.6, 172.6 ppm. MS (EI): *m*/*z* (%) = 250 (15) [M – $CH_2CH{=}CH_2$]$^+$, 91 (100). MS (CI): *m*/*z* = 292 [M + 1]$^+$. HRMS (EI): calcd. for $C_{14}H_{20}NO_3$ [M – $CH_2CH{=}CH_2$]$^+$ 250.1442; found 250.1458.

Methyl 2-Amino-2-methylbutanoate (9): In a flask was placed Pd-C (5%, 0.01 g), **6a** (0.119 g, 0.5 mmol), and anhydrous EtOH (5 mL). Then, hydrogen gas was introduced to the flask at an initial pressure of about 1 atm. The suspension was stirred for 5 h at ambient temperature. After filtration and evaporation of EtOH, the residue was subjected to column chromatography on silica gel (eluent: CH_2Cl_2) to afford **9** as a colorless oil (0.046 g, 70%). ^{1}H NMR: δ = 0.85 (t, *J* = 7.2 Hz, 3 H, *CH*$_3$CH$_2$), 1.29 (s, 3 H, *CH*$_3$CCOOCH$_3$), 1.58 (q, *J* = 7.2 Hz, 2 H, CH$_3$*CH*$_2$), 2.55 (s, 2 H, NH$_2$), 3.70 (s, 3 H, COO*CH*$_3$) ppm. ^{13}C NMR: δ = 8.15, 25.10, 34.61, 52.0, 69.5, 176.2 ppm. HRMS (EI): calcd. for $C_6H_{13}NO_2$ [M$^+$] 131.0946; found 131.0959.

Methyl 2-(Benzylamino)-2-methyl-4-pentenoate (11): To a CH_2Cl_2 solution (10 mL) of **10** (0.191 g, 1 mmol) which was obtained from methyl pyruvate and benzylamine by the usual method, $BF_3{\cdot}OEt_2$ (1 mmol) was added at 0 °C under a nitrogen atmosphere and the solution was stirred for 10 min. To this was added a triallylzincate solution that was generated via stirring for 1 h after the addition of allylmagnesium bromide (1 mmol/1 mL, 3 mL) to a CH_2Cl_2 solution (2 mL) of $ZnCl_2$ (1 mmol) in another flask. After stirring for 24 h at 0 °C, the reaction mixture was worked up according to the procedure described for the formation of **4a** to afford **11** (0.044 g, 19%) as a colorless oil. ^{1}H NMR: δ = 1.37 (s, 3 H, *CH*$_3$CCOOCH$_3$), 2.17 (s, 1 H, NH), 2.40–2.52 (m, 2 H, *CH*$_2$CH=CH$_2$), 3.61 (d, *J* = 12.0 Hz, 1 H, N*CH*$_2$Ph), 3.68 (d, *J* = 12.0 Hz, 1 H, N*CH*$_2$Ph), 3.73 (s, 3 H, COOCH$_3$), 5.10–5.14 (m, 2 H, *CH*$_2$=CH), 5.72–5.83 (m, 1 H, CH$_2$=*CH*), 7.34 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 21.8, 43.4, 48.4, 51.7, 62.1, 118.5, 126.7, 128.0, 128.1, 132.4, 139.7, 175.9 ppm. HRMS (EI): calcd. for $C_{14}H_{19}NO_2$ [M$^+$] 233.1414; found 233.1384.

Ethyl (*E*)-2-Amino-4-oxo-2-pentenoate (14): To a MeOH solution (10 mL) of **12a** (0.700 g, 5 mmol), an aqueous solution (3 mL) of hydroxylammonium chloride (5 mmol) was added. Then an aqueous solution (5 mL) of sodium carbonate (5 mmol) was added at 0 °C to the resulting solution. After stirring for 2 h at 0 °C, MeOH was mostly removed under reduced pressure and the residue was extracted with $CHCl_3$. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (eluent: CH_2Cl_2) to afford **13** (0.628 g, 81%) as a clorless oil. ^{1}H NMR: δ = 1.32 (t, *J* = 7.2 Hz, 3 H, *CH*$_3$CH$_2$), 2.29 (s, 3 H, CH$_3$C=C), 4.32 (q, *J* = 7.2 Hz, 2 H, CH$_3$*CH*$_2$), 6.72 (s, 1 H, C=CH) ppm. ^{13}C NMR: δ = 11.5, 12.8, 62.2, 109.9, 157.0, 159.6, 160.1 ppm. MS (EI): *m*/*z* (%) = 155 (16) [M$^+$], 127 (27), 110 (90), 82 (100).

According to the procedure described for the formation of **9**, **13** (0.155 g, 1 mmol) was hydrogenated in a EtOH solution (10 mL) in the presence of Pd-C (5%, 0.02 g) to afford **14** (0.119 g, 76%) as a colorless oil. ^{1}H NMR: δ = 1.29 (t, *J* = 7.2 Hz, 3 H, COOCH$_2$*CH*$_3$), 2.02 (s, 3 H, CH$_3$CO), 4.22 (q, *J* = 7.2 Hz, 2 H, COO*CH*$_2$CH$_3$), 5.77 (s, 1 H, CH=C), 6.25 (s, 2 H, NH$_2$) ppm. ^{13}C NMR: δ = 14.2, 22.8, 61.7, 94.2, 163.6, 167.6, 188.4 ppm. HRMS (EI): calcd. for $C_7H_{11}NO_3$ [M$^+$] 157.0738; found 157.0717.

Preparation of Ethyl 2-(Benzyloxyimino)-5,5-dimethyl-4-oxohexanoate (15): An aqueous solution (5 mL) of NaOH (0.2 g, 5 mmol) was added to a mixture composed of an aqueous solution (10 mL) of *O*-benzylhydroxylammonium chloride (0.798 g, 5 mmol) and CH_2Cl_2 (10 mL). The organic layer was separated and added to a CH_2Cl_2 solution (10 mL) of **12 b** (0.910 g, 5 mmol) at 0 °C. After stirring for 12 h at 0 °C, CH_2Cl_2 was almost removed under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent: CH_2Cl_2) to afford **15** (1.174 g, 77%) as a colorless oil. ^{1}H NMR: δ = 1.13 [s, 9 H, (*CH*$_3$)$_3$C], 1.33 (t, *J* = 7.0 Hz, 3 H, *CH*$_3$CH$_2$), 3.84 (s, 2 H, O=CCH$_2$C=N), 4.31 (q, *J* = 7.0 Hz, 2 H, CH$_3$*CH*$_2$), 5.28 (s, 2 H, CH$_2$Ph), 7.34 (br. s, 5 H, Ph) ppm. MS (EI): *m*/*z* (%) = 305 (5) [M$^+$], 221 (10), 206 (15), 91 (100), 57 (70).

Methyl 1-(Benzyloxy)-2-ethylpyrrolidine-2-carboxylate (18): A CH_2Cl_2 solution (10 mL) of *O*-benzylhydroxylamine generated via treatment of *O*-benzylammonium chloride (5 mmol) with an aqueous NaOH solution as described above was added at ambient temperature to a MeOH solution (15 mL) of **17**[22] (1.045 g, 5 mmol). After stirring for 24 h at ambient temperature, the solvent was removed under reduced pressure. The residue was subjected to column chromatography (eluent: CH_2Cl_2/hexane, 1:1) to afford **16** (1.444 g, 92%) as a colorless oil. ^{1}H NMR: δ = 2.14–2.21 (m, 2 H, CH$_2$*CH*$_2$CH$_2$), 2.74 (t, *J* = 7.4 Hz, 2 H, CH$_2$C=N), 3.47 (t, *J* = 6.4 Hz, 2 H, CH$_2$Br), 3.69 (s, 3 H, COOCH$_3$), 5.30 (s, 2 H, CH$_2$Ph), 7.38 (br. s, 5 H, Ph) ppm. MS (EI): *m*/*z* (%) = 91 (100) [PhCH$_2$]$^+$. MS (CI): *m*/*z* = 316 [M(^{81}Br) + 1]$^+$, 314 [M(^{79}Br) + 1]$^+$.

According to the procedure described for the formation of **4a**, **18** was obtained by the reaction of **16** (0.314 g, 1 mmol) with triethylzincate (2 mmol) as a colorless oil (0.203 g, 77%). ^{1}H NMR: δ = 0.81 (t, *J* = 7.6 Hz, 3 H, *CH*$_3$CH$_2$), 1.42–1.99 (m, 6 H, CH$_3$*CH*$_2$, NCH$_2$*CH*$_2$*CH*$_2$), 3.06–3.12 (m, 2 H, NCH$_2$), 3.65 (s, 3 H, COOCH$_3$), 4.64 (d, *J* = 11.0 Hz, 1 H, *CH*Ph), 4.70 (d, *J* = 11.0 Hz, 1 H, *CH*Ph), 7.27 (br. s, 5 H, Ph) ppm. ^{13}C NMR: δ = 7.9, 26.2, 28.0, 38.6, 52.0, 56.5, 69.8, 83.1, 127.1, 127.6, 128.0, 137.2, 175.2 ppm. HRMS (EI): calcd. for $C_{15}H_{21}NO_3$ [M$^+$] 263.1520; found 263.1539.

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