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Synthesis of α,α-disubstituted amino acids based on tandem reaction of dehydroamino acid derivatives

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Abstract—The formation of all-substituted sp^3-hybridized carbon-center was investigated via tandem reaction of dehydroamino acid derivatives. The diethylzinc-promoted reaction of dehydroamino acid derivatives with acid anhydride or π-allyl palladium complex proceeded smoothly to afford α,α-disubstituted amino acids via a radical and anionic carbon–carbon bond-forming processes. The tandem reductive reaction of *N*-phthaloyl dehydroalanine also proceeded effectively by using Bu_3SnH and $Pd(PPh_3)_4$.

1. Introduction

Non-proteinogenic α,α-disubstituted amino acids, which restrict the conformational flexibility of the peptide, have been attracting considerable attention in view of their biological and medicinal properties.[1] Therefore, the development of efficient methods for preparing all-substituted sp^3-hybridized carbon-center has become a great importance.[1] Diphenylimino glycinate **1** is an useful anionic synthon for the synthesis of α-monosubstituted amino acids, and extensive synthetic studies on the α-alkylation of **1** have been conducted (Fig. 1).[2] In contrast, the difficulty of achieving the α-alkylation of α-substituted diphenylimino esters **2** has remained unsolved due to poor acidic property of α-hydrogen atom of **2**.[3] As an alternative approach to α-substituted enolate anion **A**, we have studied the tandem reaction of dehydroamino acid derivative **3**, providing a new and efficient method for the synthesis of α,α-disubstituted amino acids.[4]

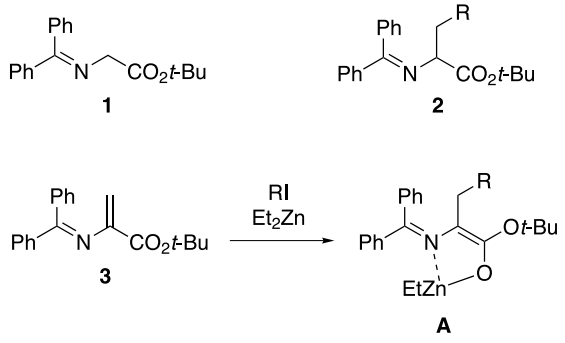

Figure 1. Anionic synthon for the synthesis of amino acids.

Multiple carbon–carbon bond formation based on tandem radical reaction is of great significance from economical and ecological points of view. In recent years, numerous radical methodologies have been reported.[5,6] However, tandem radical and anionic reactions are not well explored. Oshima's group has demonstrated that tandem radical addition-aldol condensations of enones or enals could be performed by Et_3B as a radical initiator.[7] Recently, some tandem radical and anionic reactions have been achieved.[8] Dehydroamino acid derivatives are well known to be excellent radical acceptors.[9] We report here in detail the synthesis of α,α-disubstituted amino acids based on the tandem radical and anionic reactions of dehydroamino acid derivative **3**.[4] We also report the reductive reaction of *N*-phthaloyl dehydroalanine using Bu_3SnH and $Pd(PPh_3)_4$.

2. Results and discussion

2.1. Free radical-mediated tandem reaction of dehydroamino acid derivative 3

At first, we investigated the formation of α-substituted enolate anion **A** from dehydroamino acid derivative **3** by using acid anhydrides as electrophiles (Scheme 1). The radical initiators of choice were Et_2Zn and Et_2B because of the exceptional tolerance of other functional groups.[5,6] To a

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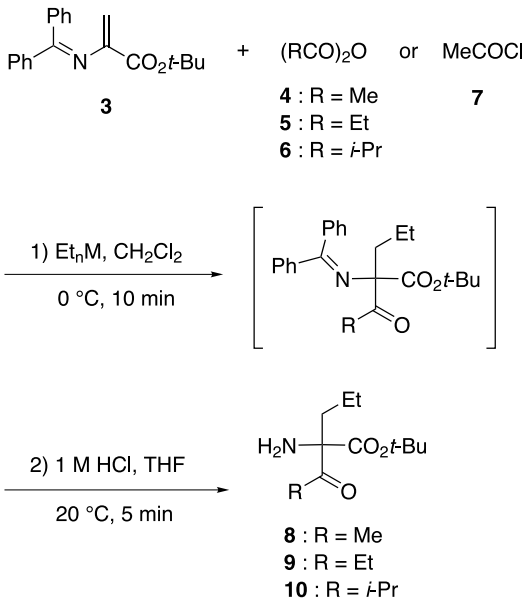


Scheme 1.

not proceed when Et_3B was employed as an ethyl radical source (entry 2). The failure of reaction with Et_3B may be attributed due to the low reactivity of Et_3B toward the radical α to an ester group.[12] Therefore, the reaction of **3** having an α,β-unsaturated ester moiety did not proceed when Et_3B was employed as an ethyl radical source. The tandem reaction with acid anhydrides **5** and **6** gave the products **9** and **10** by using Et_2Zn (entries 3 and 4). In addition, acetyl chloride **7** also worked well under the similar reaction conditions (entry 5).

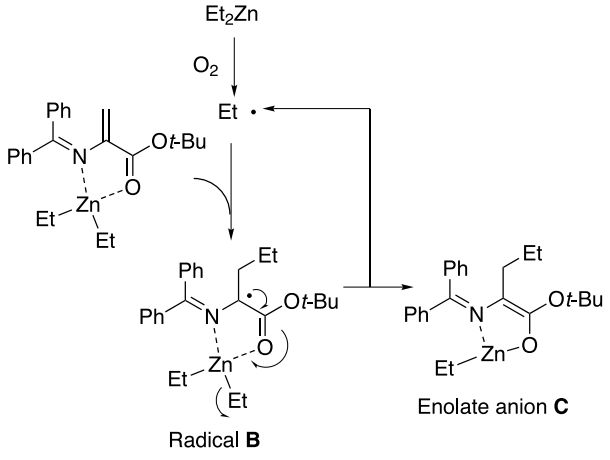
As a major reaction pathway, the α-substituted zinc-enolate anion **C** would be generated via the oxgen-initiated radical mechanism as shown in Scheme 2.[13] Initially, an ethyl radical was generated from Et_2Zn and O_2, and then, the ethyl radical added to dehydroamino acid **3** to give the intermediate radical **B**. In this reaction, Et_2Zn acted as an effective reagent for trapping the intermediate radical **B** to give the zinc-enolate anion **C** and an ethyl radical. Recently, the formation of zinc enolates from α,β-unsaturated esters in diethylzinc-mediated radical reactions was reported by Bertrand's group.[8b]

Table 1. Tandem reaction of dehydroamino acid derivative **3**[a]

Entry	Et_nM	Reagent	Product	Yield (%)[b]
1	Et_2Zn	**4**	**8**	63
2	Et_3B	**4**		No detection
3	Et_2Zn	**5**	**9**	43
4	Et_2Zn	**6**	**10**	41
5	Et_2Zn	**7**	**8**	56

[a] Reactions were carried out with **3** (1 equiv), **4**–**7** (1.2 equiv) and Et_2Zn (1.5 equiv) in CH_2Cl_2.
[b] Isolated yields after hydrolysis of diphenylimino group.

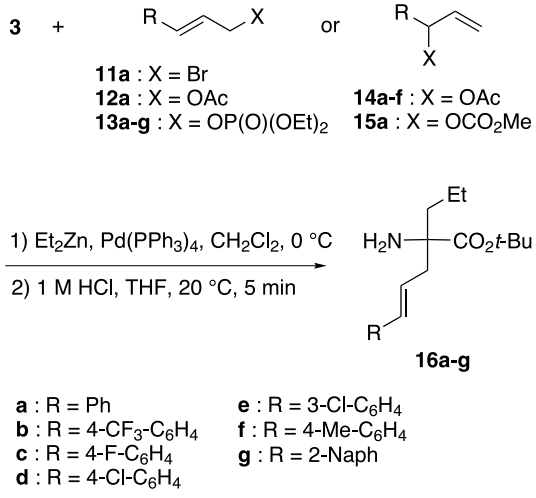
solution of dehydroamino acid derivative **3** and acetic anhydride **4** (1.2 equiv) in CH_2Cl_2 was added a 1.0 M solution of Et_2Zn in hexane (1.5 equiv) at 0 °C (Table 1, entry 1). As expected, dehydroamino acid derivative **3** exhibited a good reactivity toward Et_2Zn to give the desired α,α-disubstituted amino acid **8** in 63% yield, after hydrolysis of diphenylimino moiety. A trace amount of O_2 was an essential source for successful reaction.[10,11] Thus, the reaction was carried out by using undegassed dry solvent under Ar. In marked contrast, the tandem reaction of **3** did



Scheme 2.

2.2. Combination of radical reaction and transition metal-catalyzed reaction

On the basis of tandem acylation reaction, we next investigated the tandem allylation reaction of **3** by using different types of electrophiles **11a**–**15a** (Scheme 3). In the absence of palladium catalyst, the diethylzinc-promoted reaction of **3** with cinnamyl bromide **11a** did not give the allylated product **16a** (Table 2, entry 1). The electrophilic



Scheme 3.

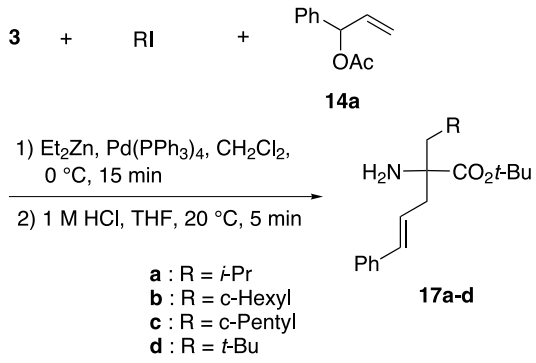
Table 2. Tandem palladium-catalyzed reaction of **3** with **11a–15a**[a]

Entry	Et_nM	Catalyst	Reagent	Time (min)	Product	Yield (%)[b]
1	Et_2Zn	None	**11a**	60	**16a**	No detection
2	Et_2Zn	$Pd(PPh_3)_4$	**11a**	60	**16a**	29
3	Et_2Zn	$Pd(PPh_3)_4$	**12a**	20	**16a**	54
4	Et_2Zn	$Pd(PPh_3)_4$	**13a**	20	**16a**	61
5	Et_2Zn	$Pd(PPh_3)_4$	**14a**	20	**16a**	59
6	Et_2Zn	$Pd(PPh_3)_4$	**15a**	20	**16a**	45
7	Et_3B	$Pd(PPh_3)$	**13a**	60		No detection
8	Et_3B	$Pd(PPh_3)_4$	**14a**	60		No detection
9	Et_2Zn	$Pd(PPh_3)_4$	**13b**	20	**16b**	40
10	Et_2Zn	$Pd(PPh_3)_4$	**13c**	20	**16c**	51
11	Et_2Zn	$Pd(PPh_3)_4$	**13d**	20	**16d**	61
12	Et_2Zn	$Pd(PPh_3)_4$	**13e**	20	**16e**	56
13	Et_2Zn	$Pd(PPh_3)_4$	**13f**	20	**16f**	47
14	Et_2Zn	$Pd(PPh_3)_4$	**13g**	20	**16g**	46
15	Et_2Zn	$Pd(PPh_3)_4$	**14d**	20	**16d**	68
16	Et_2Zn	$Pd(PPh_3)_4$	**14e**	20	**16e**	46
17	Et_2Zn	$Pd(PPh_3)_4$	**14f**	20	**16f**	41

[a] Reactions were carried out with **3** (1 equiv), **11a–15a** (1.5 equiv), and Et_2Zn (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (0.15 equiv).
[b] Isolated yields after hydrolysis of diphenylimino group.

π-allyl palladium complex has shown excellent reactivity toward soft carbanions. Thus, we next studied the diethylzinc-promoted reaction of **3** with π-allyl palladium complex.[14] To a solution of dehydroamino acid derivative **3**, cinnamyl bromide **11a**, and $Pd(PPh_3)_4$ (0.15 equiv) in CH_2Cl_2 was added Et_2Zn at 0 °C, and then the reaction mixture was stirred for 60 min (entry 2). As expected, the formation of the allylated product **16a** was observed in the presence of $Pd(PPh_3)_4$, after hydrolysis of diphenylimino moiety. To see the effect of allylic reagents, we investigated the reactions with precursors **12a–15a**. Among them, phosphate **13a** and branched acetate **14a** were found to be effective for tandem allylation reaction of **3** (entries 3–6). The reaction of **3** with phosphate **13a** proceeded smoothly in the presence of $Pd(PPh_3)_4$ to give the allylated product **16a** in 61% yield, after being stirred at 0 °C for only 20 min (entry 4). The reaction with the branched acetate **14a** also gave the product **16a** in 59% yield, after hydrolysis of diphenylimino moiety (entry 5). The tandem allylation reaction of **3** did not proceed when Et_3B was employed as an ethyl radical source (entries 7 and 8). The tandem reaction of **3** was performed with other π-allyl palladium complexes (entries 9–17). The reactions of **3** with aromatic allylic phosphates **13b–g** and branched acetates **14d–f** were carried out in the presence of $Pd(PPh_3)_4$ (0.15 equiv). As expected, the tandem allylation reaction proceeded smoothly to give the α,α-disubstituted amino acids **16b–g**, allowing facile incorporation of structural variety. The present reaction is the first example of a combination of radical reaction and transition metal-catalyzed allylation in tandem carbon–carbon bond-forming process.

With the optimal allylic reagent **14a**, three-component reaction using several radical precursors (RI) was examined (Scheme 4). The isopropylated amino acid derivative **17a** was obtained in 56% yield by using *i*-PrI (Table 3, entry 1). Other secondary alkyl radical precursors such as *c*-pentyl-I and *c*-hexyl-I worked well to give the desired products **17b–c** (Table 3, entries 2 and 3). The reaction with a bulky *tert*-butyl radical also gave the allylated amino acid **17d** in 30% yield (entry 4). These results supported the radical mechanism. A favorable experimental feature of this radical method is that the reaction proceeded smoothly even in the absence of toxic tin hydride or heavy metals via the iodine atom-transfer radical process as shown in Scheme 5.



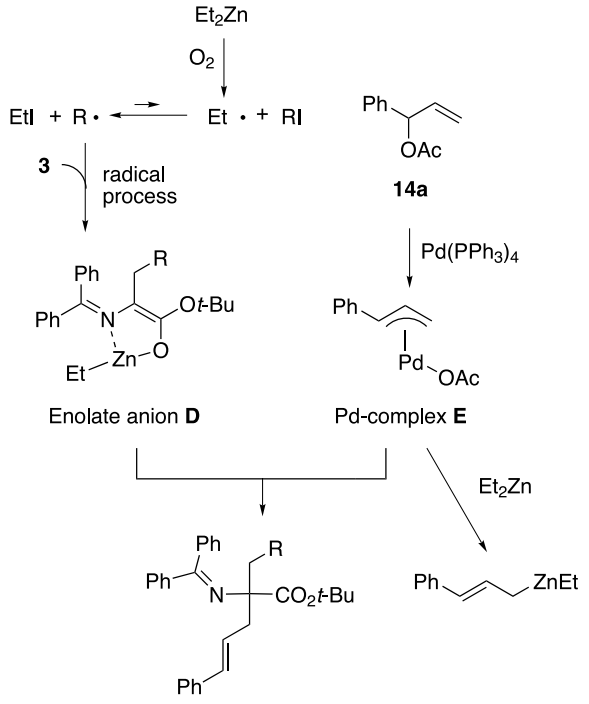
Scheme 4.

Table 3. Tandem palladium-catalyzed reaction of **3** with **14a** and RI[a]

Entry	RI	Product	Yield (%)[b]
1	*i*-PrI	**17a**	56
2	c-Hexyl I	**17b**	56
3	c-Pentyl I	**17c**	58
4	*t*-Bu I	**17d**	30

[a] Reactions were carried out with **3** (1 equiv), **14a** (2.0 equiv), RI (30 equiv), and Et_2Zn (3.0 equiv) in the presence of $Pd(PPh_3)_4$ (0.3 equiv).
[b] Isolated yields after hydrolysis of diphenylimino group.

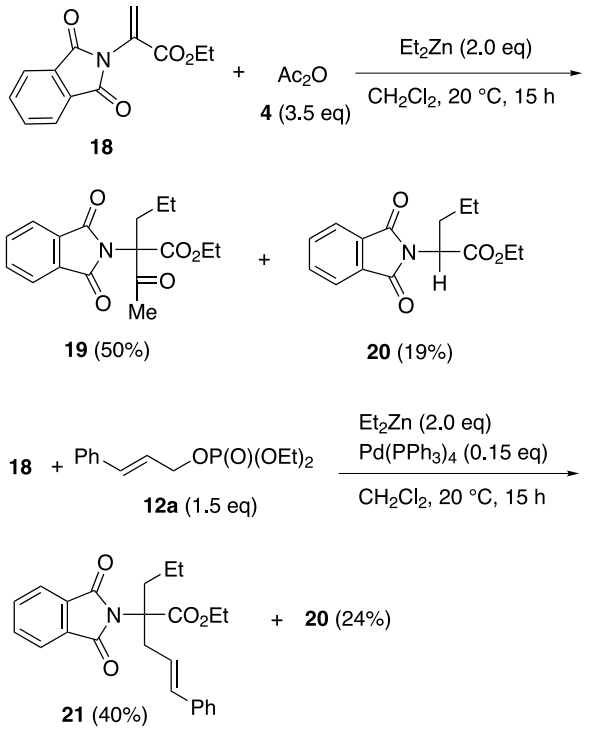
The following points should be noted for the success of the present tandem allylation: (I) a high reactivity of Et_2Zn as a radical initiator, (II) an excellent intermolecular reactivity of dehydroamino acid derivative **3** as a radical acceptor, and (III) a high reactivity of Et_2Zn as a trapping reagent toward the alkoxycarbonyl-stabilized α-radical **B** (Scheme 2). The reactivity of dehydroamino acid derivative **3** toward Et_2Zn is also important, because the reaction of electrophilic π-allyl palladium complex **E** with Et_2Zn could give the allyl zinc reagent as a by-product (Scheme 5).[15]



Scheme 5.

2.3. Reaction of *N*-phthaloyl dehydroalanine and its application to tandem reductive reaction

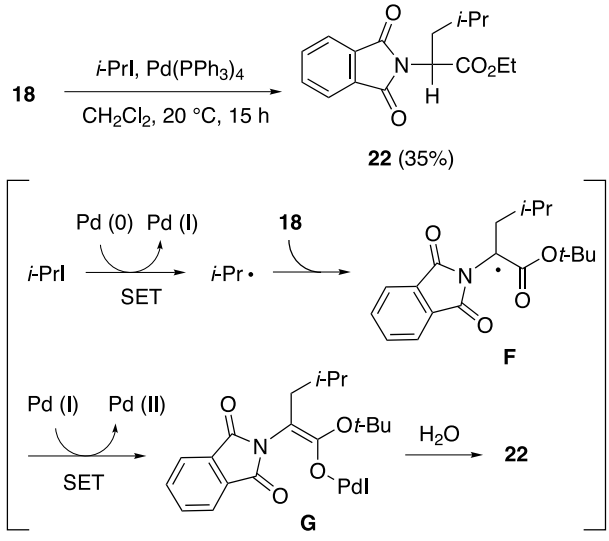
In the case of dehydroamino acid derivative **3**, it was assumed that a stable 5-membered zinc-enolate anion **D** is formed as a result of the coordination with nitrogen atom of diphenylimino group. We next investigated the reaction of *N*-phthaloyl dehydroalanine **18**,[9b,d] which would not give the stable coordinating zinc-enolate anion (Scheme 6). We expected that the direct comparison of **3** with **18** would lead to informative and instructive suggestions regarding the combination of radical reaction and transition metal-catalyzed allylation.



Scheme 6.

The diethylzinc-promoted reaction of *N*-phthaloyl dehydroalanine **18** was investigated by using acetic anhydride as an electrophile. In marked contrast to the excellent reactivity of dehydroamino acid derivative **3**, the tandem acylation reaction of **18** proceeded slowly to give the desired product **19** in 50% yield, accompanied with a 19% yield of the protonated product **20**, after being stirred at 20 °C for 15 h. The tandem allylation reaction of **18** with **12a** was investigated in the presence of $Pd(PPh_3)_4$ (0.15 equiv). Although the desired allylated product **21** was obtained in 40% yield, the tandem allylation of **18** also proceeded with a low chemical efficiency.

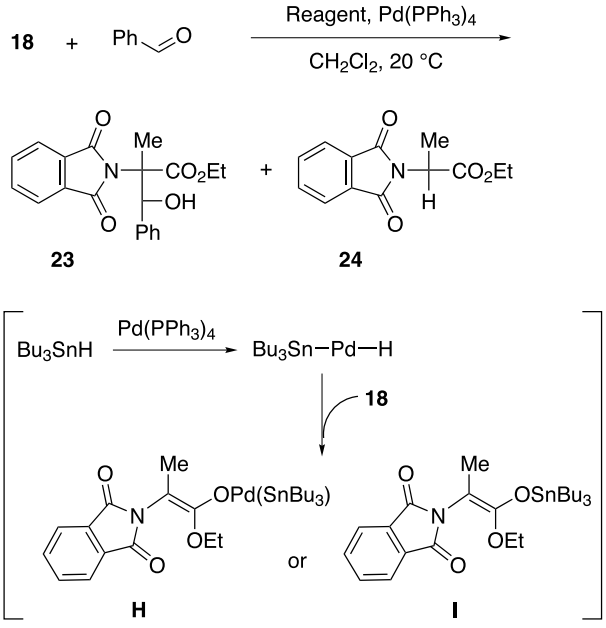
We also investigated the tandem allylation of **18** by using radical precursors such as *i*-PrI or *tert*-BuI. However, the palladium-catalyzed allylation of less reactive *N*-phthaloyl dehydroalanine **18** did not proceed effectively in the presence of alkyl iodides. The formation of the desired products was not observed, probably due to deactivation of $Pd(PPh_3)_4$ by alkyl iodides. As an important effect of palladium catalyst, D. P. Curran reported the palladium (0)-promoted radical cyclization of unsaturated α-iodocarbonyl compounds.[16] These results indicated that $Pd(PPh_3)_4$ serves as a radical initiator, and thus, the deactivation of $Pd(PPh_3)_4$ would proceed via the single-electron transfer (SET) process from palladium (0) to alkyl iodides. In order to test the viability of $Pd(PPh_3)_4$ as a radical initiator, the simple isopropyl radical addition to **18** was investigated (Scheme 7). As expected, $Pd(PPh_3)_4$ served as a single-electron transfer radical initiator to afford the isopropylated product **22** in 35% yield. These results indicate that the success of tandem allylation of **3** using radical precursors reflects the excellent reactivity of **3**.



Scheme 7.

The reductive aldol reactions are attractive reaction, since a reductive method does not require preformation of metal enolates or silyl enol ethers.[17] Therefore, construction

of all-substituted sp^3-hybridized carbon-center via a reductive process is a challenging problem. As an alternative approach to α-substituted enolate anion, we finally investigated the reductive aldol reaction of **18** (Scheme 8). In the presence of $Pd(PPh_3)_4$, the reductive aldol reaction of **18** with benzaldehydride was studied (Table 4). Among several reducing reagents evaluated, Bu_3SnH was found to be the most effective for the reductive aldol reaction of **18** to afford the desired product **23** in 65% yield, accompanied with 16% yield of the protonated product **24** (entry 1). The reaction would proceed via enolate anion **H** or **I** generated from $Pd(PPh_3)_4$ and Bu_3SnH.



Scheme 8.

Table 4. Reductive tandem reaction of **18** with benzaldehyde[a]

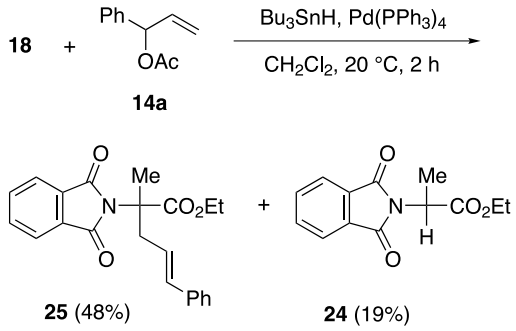
Entry	Reagent	Time (h)	Product (% yield)[b]
1	Bu_3SnH	2	**23** (65%), **24** (16%)
2	Et_3SiH	24	No reaction
3	$Cl(i\text{-}Pr)_2SiH$	24	No reaction
4	$(TMS)_3SiH$	24	**24** (72%)

[a] Reactions were carried out with **18** (1 equiv), reagent (1.2 equiv), and benzaldehyde in the presence of $Pd(PPh_3)_4$ (0.1 equiv).
[b] Isolated yields.

To survey the scope of the present method, the reductive allylation reaction of **18** was studied by using the branched acetate **14a** (Scheme 9). The allylation proceeded smoothly to give the desired product **25** in 48% yield. In addition to the diethylzinc-promoted tandem reactions, the reductive reactions disclosed a broader aspect of the utility of dehydroamino acids for the synthesis of α,α-disubstituted amino acids.

3. Conclusion

We have demonstrated the formation of α-substituted



Scheme 9.

enolate anions from dehydroamino acid derivative **3** or *N*-phthaloyl dehydroalanine **18**. The diethylzinc-promoted tandem reaction of **3** gave the α,α-disubstituted amino acids by using acid anhydrides or π-allyl palladium complexes as electrophiles. A remarkable feature of this reaction is the construction of all-substituted sp^3-hybridized carbon-center via a tandem process, which involves the sequential two steps of carbon–carbon bond forming reactions. The reductive reaction of **18** proceeded smoothly in the presence of Bu_3SnH and $Pd(PPh_3)_4$ to give α,α-disubstituted amino acid derivatives.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz and at 125 MHz, respectively; chemical shifts are measured in ppm. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI, CI, or FAB methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$).

4.2. Typical experimental procedure for tandem reaction of dehydroamino acid derivative 3 with acid anhydride 4–6 or acetyl chloride 7

To a solution of **3** (1.00 g, 3.26 mmol) and acid anhydride **4–6** or acetyl chloride **7** (3.91 mmol) in CH_2Cl_2 (50 mL) was added Et_2Zn (1.0 M in hexane, 4.89 mL, 4.89 mmol) at 0 °C. After being stirred at the same temperature for 10 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (30 mL), and then 1 M HCl (20 mL) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane–AcOEt=5:1) afforded **8–10**.

4.2.1. *tert*-Butyl 2-acetyl-2-aminopentanoate (8). A colorless oil. IR ($CHCl_3$) 3399, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.23 (3H, s), 1.96 (1H, m), 1.86 (2H, br s), 1.77 (1H, m), 1.47 (9H, s), 1.27 (2H, br sex, J=7.6 Hz), 0.95 (3H, t, J=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 205.6, 171.0, 82.6, 71.3, 37.8, 27.7, 25.1, 16.8, 14.3.

4.2.2. *tert*-Butyl 2-amino-3-oxo-2-propylpentanoate (9). A colorless oil. IR ($CHCl_3$) 3400, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.64 (1H, m), 2.51 (1H, m), 1.93 (1H, m), 1.88 (2H, br s), 1.78 (1H, m), 1.46 (9H, s), 1.25 (2H, m), 1.08 (3H, t, J=7.7 Hz), 0.95 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 208.2, 171.0, 82.2, 70.9, 37.5, 30.3, 27.5, 16.6, 14.0, 7.9. MS (CI^+) *m/z*: 230 ($M+H^+$, 1.1), 116 (100). HRMS calcd for $C_{12}H_{24}NO_3$ ($M+H^+$) 230.1756, found 230.1761.

4.2.3. *tert*-Butyl 2-amino-4-methyl-3-oxo-2-propylpentanoate (10). A colorless oil. IR ($CHCl_3$) 3432, 1724, 1668 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.96 (1H, br m), 4.49 (1H, br m), 2.40 (1H, m), 1.79 (1H, m), 1.61 (1H, m), 1.47 (9H, s), 1.34 (2H, m), 1.17 (3H, d, J=6.7 Hz), 1.16 (3H, t, J=6.7 Hz), 0.93 (3H, t, J=7.3 Hz). MS (CI^+) *m/z*: 244 ($M+H^+$, 0.6), 72 (100). HRMS calcd for $C_{13}H_{25}NO_3$ ($M+H^+$) 244.1913, found 244.1908.

4.3. Typical experimental procedure for tandem reaction of dehydroamino acid derivative 3 with allyic reagent 11–15

To a solution of **3** (100 mg, 0.32 mmol), allylic reagent **11–15** (0.48 mmol), and $Pd(PPh_3)_4$ (56 mg, 0.048 mmol) in CH_2Cl_2 (4 mL) was added Et_2Zn (1.0 M in hexane, 0.48 mL, 0.48 mmol) at 0 °C. After being stirred at the same temperature for 20–60 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (4 mL), and then 1 M HCl (2 mL) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$) afforded **16a–g**.

4.3.1. (*E*)-*tert*-Butyl 2-amino-5-phenyl-2-propylpent-4-enoate (16a). A colorless oil. IR ($CHCl_3$) 3366, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33–7.21 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.11 (1H, m), 2.67 (1H, dd, J=13.4, 6.4 Hz), 2.36 (1H, dd, J=13.4, 8.5 Hz), 1.74 (1H, m), 1.68 (2H, br s), 1.52 (1H, m), 1.48 (9H, s), 1.45–1.25 (2H, m), 0.93 (3H, t, J=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 176.1, 137.2, 134.1, 128.5, 127.3, 126.2, 124.6, 81.0, 61.2, 43.7, 42.5, 28.0, 17.2, 14.4. MS (FAB^+) *m/z*: 290 ($M+H^+$, 43), 234 (100). HRMS calcd for $C_{18}H_{28}NO_2$ ($M+H^+$) 290.2120, found 290.2123.

4.3.2. (*E*)-*tert*-Butyl 2-amino-5-(4-(trifluoromethyl)-phenyl)-2-propylpent-4-enoate (16b). A colorless oil. IR ($CHCl_3$) 3395, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.54 (2H, d, J=8.2 Hz), 7.41 (2H, d, J=8.2 Hz), 6.51 (1H, d, J=15.9 Hz), 6.25 (1H, m), 2.68 (1H, dd, J=13.7, 6.7 Hz), 2.40 (1H, dd, J=13.7, 8.4 Hz), 1.75 (1H, m), 1.70 (2H, br s), 1.54 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.24 (1H, m), 0.94 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 175.9, 140.6, 132.6, 129.2 (q, J=32 Hz), 127.7, 126.3, 125.5, 124.2 (q, J=271 Hz), 81.1, 61.2, 43.7, 42.4, 28.0, 17.1, 14.4. MS (CI^+) *m/z*: 358 ($M+H^+$, 0.8), 116 (100). HRMS calcd for $C_{19}H_{27}F_3NO_2$ ($M+H^+$) 358.1994, found 358.1989.

4.3.3. (*E*)-*tert*-Butyl 2-amino-5-(4-fluorophenyl)-2-propylpent-4-enoate (16c). A colorless oil. IR ($CHCl_3$) 3395, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33–7.22 (2H, m), 6.99 (2H, br t, J=8.6 Hz), 6.44 (1H, d, J=15.9 Hz), 6.02 (1H, m), 2.64 (1H, dt, J=13.4, 6.7 Hz), 2.35 (1H, dt, J=13.4, 8.2 Hz), 1.77 (1H, m), 1.73 (2H, br s), 1.52 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.23 (1H, m), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 176.3, 162.5 (d, J=246 Hz), 133.6, 133.1, 127.9 (d, J=7.2 Hz), 124.6, 115.7 (d, J=22 Hz), 81.3, 61.4, 43.9, 42.7, 28.3, 17.4, 14.7. MS (CI^+) *m/z*: 308 ($M+H^+$, 0.6), 116 (100). HRMS calcd for $C_{18}H_{27}FNO_2$ ($M+H^+$) 308.2026, found 308.2030.

4.3.4. (*E*)-*tert*-Butyl 2-amino-5-(4-chlorophenyl)-2-propylpent-4-enoate (16d). A colorless oil. IR ($CHCl_3$) 3413, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31–7.20 (4H, m), 6.43 (1H, d, J=15.9 Hz), 6.10 (1H, m), 2.65 (1H, dd, J=13.7, 6.7 Hz), 2.36 (1H, dd, J=13.7, 8.2 Hz), 1.75 (1H, m), 1.70 (2H, br s), 1.52 (1H, m), 1.47 (9H, s), 1.41 (1H, m), 1.23 (1H, m), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 175.9, 135.7, 132.9, 132.8, 128.7, 127.4, 125.4, 81.0, 61.2, 43.7, 42.4, 28.0, 17.1, 14.4. MS (CI^+) *m/z*: 324 ($M+H^+$, 0.5), 116 (100). HRMS calcd for $C_{18}H_{27}ClNO_2$ ($M+H^+$) 324.1730, found 324.1729.

4.3.5. (*E*)-*tert*-Butyl 2-amino-5-(3-chlorophenyl)-2-propylpent-4-enoate (16e). A colorless oil. IR ($CHCl_3$) 3394, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31 (1H, s), 7.25–7.14 (3H, m), 6.41 (1H, d, J=15.9 Hz), 6.15 (1H, m), 2.65 (1H, dd, J=13.7, 6.7 Hz), 2.37 (1H, dd, J=13.7, 8.4 Hz), 1.76 (1H, m), 1.73 (2H, br s), 1.51 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.22 (1H, m), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 176.1, 139.3, 134.7, 132.9, 130.0, 127.5, 126.6, 126.4, 124.6, 81.3, 61.4, 43.9, 42.6, 28.3, 17.4, 14.6. MS (CI^+) *m/z*: 324 ($M+H^+$, 0.6), 116 (100). HRMS calcd for $C_{18}H_{27}ClNO_2$ ($M+H^+$) 324.1730, found 324.1729.

4.3.6. (*E*)-*tert*-Butyl 2-amino-2-propyl-5-*p*-tolylpent-4-enoate (16f). A colorless oil. IR ($CHCl_3$) 3427, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.21 (2H, d, J=7.6 Hz), 7.09 (2H, d, J=7.6 Hz), 6.45 (1H, d, J=15.6 Hz), 6.05 (1H, m), 2.66 (1H, dd, J=13.6, 6.6 Hz), 2.34 (1H, dd, J=13.6, 8.4 Hz), 2.32 (3H, s), 1.74 (1H, m), 1.69 (2H, br s), 1.51 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.22 (1H, m), 0.93 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 175.9, 136.9, 134.2, 133.7, 129.0, 125.8, 123.2, 80.7, 60.9, 43.5, 42.2, 27.8, 20.8, 16.9, 14.2. MS (CI^+) *m/z*: 304 ($M+H^+$, 0.6), 116 (100). HRMS calcd for $C_{19}H_{30}lNO_2$ ($M+H^+$) 304.2276, found 304.2281.

4.3.7. (*E*)-*tert*-Butyl 2-amino-5-(naphthalen-2-yl)-2-propylpent-4-enoate (16g). A colorless oil. IR ($CHCl_3$) 3410, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.82–7.73 (3H, m), 7.67 (1H, s), 7.56 (1H, d, J=8.6 Hz), 7.43 (2H, m), 6.65 (1H, d, J=15.6 Hz), 6.25 (1H, m), 2.73 (1H, dd, J=13.7, 7.0 Hz), 2.44 (1H, dd, J=13.7, 8.9 Hz), 1.78 (1H, m), 1.71 (2H, br s), 1.57 (1H, m), 1.49 (9H, s), 1.42 (1H, m), 1.25 (1H, m), 0.95 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 175.8, 134.4, 133.9, 133.4, 132.6, 127.9, 127.7, 127.5, 126.0, 125.7, 125.5, 124.8, 123.2, 80.8, 61.0, 43.6, 42.2, 27.8, 16.9, 14.2. MS (CI^+) *m/z*: 340 ($M+H^+$, 1.5), 116 (100). HRMS calcd for $C_{22}H_{30}lNO_2$ ($M+H^+$) 340.2276, found 340.2281.

4.4. Typical experimental procedure for tandem reaction of dehydroamino acid derivative 3 with allylic reagent 14a and radical precurser

To a solution of **3** (60 mg, 0.20 mmol), allylic reagent **14a** (69 mg, 0.39 mmol), RI (5.9 mmol), and $Pd(PPh_3)_4$ (68 mg, 0.059 mmol) in CH_2Cl_2 (2 mL) was added Et_2Zn (1.0 M in hexane, 0.59 mL, 0.59 mmol) at 0 °C. After being stirred at the same temperature for 15 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (4 mL), and then 1 M HCl (1 mL) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$) afforded **17a–d** and **18**.

4.4.1. (*E*)-*tert*-Butyl 2-amino-2-isobutyl-5-phenylpent-4-enoate (17a). A colorless oil. IR ($CHCl_3$) 3391, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.18 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.09 (1H, m), 2.66 (1H, dd, J=13.0, 6.3 Hz), 2.33 (1H, dd, J=13.0, 8.7 Hz), 1.76 (2H, m), 1.66 (2H, br s), 1.53 (1H, m), 1.48 (9H, s), 0.97 (3H, d, J=5.2 Hz), 0.90 (3H, d, J=5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 176.6, 137.2, 134.3, 128.6, 127.4, 126.2, 124.3, 81.1, 60.9, 48.3, 45.3, 28.0, 24.6, 24.4, 23.3. MS (FAB^+) *m/z*: 304 ($M+H^+$, 38), 248 (100). HRMS calcd for $C_{19}H_{30}NO_2$ ($M+H^+$) 304.2276, found 304.2276.

4.4.2. (*E*)-*tert*-Butyl 2-amino-2-(cyclohexylmethyl)-5-phenylpent-4-enoate (17b). A colorless oil. IR ($CHCl_3$) 3390, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.17 (5H, m), 6.47 (1H, d, J=15.9 Hz), 6.08 (1H, m), 2.65 (1H, dd, J=13.4, 6.7 Hz), 2.33 (1H, dd, J=13.4, 8.6 Hz), 1.76 (1H, m), 1.65 (2H, br s), 1.50 (1H, m), 1.48 (9H, s), 1.45–0.88 (11H, m). ^{13}C NMR ($CDCl_3$) δ 176.3, 136.9, 134.0, 128.3, 127.1, 125.9, 124.1, 80.8, 60.6, 46.7, 44.9, 34.9, 33.8, 33.7, 27.7, 26.0 (2C), 25.9. MS (FAB^+) *m/z*: 344 ($M+H^+$, 28), 288 (100). HRMS calcd for $C_{22}H_{34}NO_2$ ($M+H^+$) 344.2589, found 344.2582.

4.4.3. (*E*)-*tert*-Butyl 2-amino-2-(cyclopentylmethyl)-5-phenylpent-4-enoate (17c). A colorless oil. IR ($CHCl_3$) 3410, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36–7.20 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.10 (1H, m), 2.68 (1H, dd, J=13.5, 6.4 Hz), 2.34 (1H, dd, J=13.5, 8.5 Hz), 1.94–1.72 (5H, m), 1.69 (2H, br s), 1.67–1.51 (4H, m), 1.48 (9H, s), 1.17 (1H, m), 1.09 (1H, m). ^{13}C NMR ($CDCl_3$) δ 176.8, 137.4, 134.5, 128.8, 127.6, 126.4, 124.7, 81.3, 61.6, 46.1, 45.0, 36.6, 34.4, 33.9, 28.3, 25.1, 25.0. MS (FAB^+) *m/z*: 330 ($M+H^+$, 57), 274 (100). HRMS calcd for $C_{21}H_{32}NO_2$ ($M+H^+$) 330.2433, found 330.2437.

4.4.4. (*E*)-*tert*-Butyl 2-amino-2-neopentyl-5-phenylpent-4-enoate (17d). A colorless oil. IR ($CHCl_3$) 2956, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34–7.20 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.05 (1H, m), 2.65 (1H, dd, J=13.4, 6.4 Hz), 2.32 (1H, dd, J=13.4, 8.9 Hz), 2.00 (1H, d, J=14.3 Hz), 1.74 (2H, br s), 1.56 (1H, d, J=14.3 Hz), 1.49 (9H, s), 1.01 (9H, s). ^{13}C NMR ($CDCl_3$) δ 176.7, 137.2, 134.6, 128.6, 127.4, 126.2, 123.9, 81.3, 61.5, 52.0, 47.4, 31.5, 31.2, 28.0. MS (FAB^+) *m/z*: 318 ($M+H^+$, 45), 262 (100). HRMS calcd for $C_{20}H_{32}NO_2$ ($M+H^+$) 318.2433, found 318.2428.

4.4.5. Ethyl 2-acetyl-2-(1,3-dioxoisoindolin-2-yl)pentanoate (19). To a solution of **18** (50 mg, 0.2 mmol) and acetic anhydride (0.07 mL, 0.71 mmol) in CH_2Cl_2 (1 mL) was added Et_2Zn (1.0 M in hexane, 0.41 mL, 0.41 mmol) at 20 °C. After being stirred at the same temperature for 15 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded **19** (32 mg, 50%) and **20** (10 mg, 19%). A colorless oil. IR ($CHCl_3$) 1782, 1719 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.74 (2H, m), 4.00 (2H, q, J=7.0 Hz), 2.48 (2H, t, J=7.6 Hz), 2.01 (3H, s), 1.42–1.28 (2H, m), 1.36 (3H, t, J=7.0 Hz), 0.93 (3H, t, J=7.0 Hz). MS (EI^+) *m/z*: 317 (M^+, 0.8), 229 (100). HRMS calcd for $C_{17}H_{19}NO_5$ (M^+) 317.1263, found 317.1258.

4.4.6. Ethyl 2-(1,3-dioxoisoindolin-2-yl)pentanoate (20). A colorless oil. IR ($CHCl_3$) 1739, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.74 (2H, m), 4.86 (1H, dd, J=11.0, 4.6 Hz), 4.21 (2H, m), 2.27 (1H, m), 2.18 (1H, m), 1.34 (2H, m), 1.23 (3H, t, J=7.0 Hz), 0.94 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 169.5, 167.8, 134.1, 131.9, 123.5, 61.7, 52.0, 30.5, 19.5, 14.0, 13.3. MS (EI^+) *m/z*: 275 (M^+, 2.2), 202 (100). HRMS calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1157, found 275.1155.

4.5.7. (*E*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-5-phenyl-2-propylpent-4-enoate (21). To a solution of **18** (50 mg, 0.20 mmol), allylic reagent **12a** (83 mg, 0.31 mmol), and $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added Et_2Zn (1.0 M in hexane, 0.41 mL, 0.41 mmol) at 20 °C. After being stirred at the same temperature for 15 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$) afforded **21** (31 mg, 40%) and **20** (16 mg, 24%). A colorless oil. IR ($CHCl_3$) 1720, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.78 (2H, m), 7.69 (2H, m), 7.26–7.12 (5H, m), 6.36 (1H, d, J=15.6 Hz), 6.14 (1H, m), 4.24 (2H, q, J=7.0 Hz), 3.31 (1H, dd, J=13.7, 6.4 Hz), 3.07 (1H, dd, J=13.7, 7.3 Hz), 2.45 (1H, m), 2.30 (1H, m), 1.35 (2H, m), 1.24 (3H, t, J=7.0 Hz), 0.96 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 171.0, 168.8, 137.2, 134.1, 131.5, 128.4, 127.3, 126.2, 124.4, 123.5, 123.2, 123.1, 67.1, 61.4, 38.0, 36.1, 30.5, 17.6, 14.2. MS (EI^+) *m/z*: 391 (M^+, 1.0), 244 (100). HRMS calcd for $C_{24}H_{25}NO_4$ (M^+) 291.1783, found 291.1779.

4.5.8. Ethyl 4-methyl-2-(1,3-dioxoisoindolin-2-yl)pentanoate (22). To a solution of **18** (100 mg, 0.41 mmol) and $Pd(PPh_3)_4$ (471 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) was added isopropyl iodide (0.40 mL, 4.1 mmol) at 20 °C. After being stirred at the same temperature for 15 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded **22** (42 mg, 35%). A colorless oil. IR ($CHCl_3$) 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.74 (2H, m), 4.94 (1H, dd, J=11.6, 4.6 Hz), 4.20 (2H, m), 2.33 (1H, m), 1.97 (1H, m), 1.50 (1H, m), 1.23 (3H, t, J=7.0 Hz), 0.96 (3H, d, J=6.4 Hz), 0.93 (3H, d, J=6.7 Hz). ^{13}C NMR ($CDCl_3$) δ 169.8, 167.9, 134.2, 131.9, 123.5, 61.8, 50.8, 37.2, 25.1, 23.1, 21.0, 14.0. MS (FAB^+) m/z: 290 ($M+H^+$, 48), 216 (100). HRMS calcd for $C_{16}H_{19}NO_4$ ($M+H^+$) 290.1393, found 290.1395.

4.5.9. Ethyl 3-hydroxy-2-methyl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (23). To a solution of **18** (50 mg, 0.20 mmol), benzaldehyde (0.04 mL, 0.41 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was added Bu_3SnH (0.07 mL, 0.25 mmol) at 20 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. After being roughly removed the tin residue by flash chromatography (hexane–AcOEt=5:1), purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded diastereomixture of **23** (46 mg, 65%) in 9:1 ratio and **24** (8 mg, 16%). Major isomer: a colorless oil. IR ($CHCl_3$) 3526, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.83–7.71 (4H, m), 7.32–7.15 (5H, m), 5.60 (1H, br s), 4.36 (1H, br s), 4.26 (2H, q, J=7.0 Hz), 1.94 (3H, s), 1.23 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 174.4, 168.3, 137.8, 134.5, 131.6, 128.5, 128.1, 127.7, 123.5, 73.8, 65.9, 62.3, 15.7, 14.1. MS (FAB^+) m/z: 354 ($M+H^+$, 21), 336 (100). HRMS calcd for $C_{20}H_{20}NO_5$ ($M+H^+$) 354.1341, found 354.1347.

4.5.10. Ethyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (24). A colorless oil. IR ($CHCl_3$) 1720, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.75 (2H, m), 4.97 (1H, q, J=7.3 Hz), 4.21 (2H, m), 1.70 (3H, d, J=7.3 Hz), 1.24 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 169.7, 167.5, 134.1, 131.9, 123.5, 61.8, 47.5, 15.2, 14.0. MS (FAB^+) m/z: 348 ($M+H^+$, 72), 174 (100). HRMS calcd for $C_{13}H_{14}NO_4$ ($M+H^+$) 248.0923, found 248.0918.

4.5.11. (*E*)-Ethyl 2-methyl-2-(1,3-dioxoisoindolin-2-yl)-5-phenylpent-4-enoate (25). To a solution of **18** (32 mg, 0.13 mmol), allylic reagent **14a** (27 mg, 0.16 mmol), and $Pd(PPh_3)_4$ (15 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) was added Bu_3SnH (0.04 mL, 0.16 mmol) at 20 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. After being roughly removed the tin residue by flash chromatography (hexane–AcOEt=5:1), purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded **25** (15 mg, 48%) and **24** (9 mg, 19%). A colorless oil. IR ($CHCl_3$) 1723, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.78 (2H, m), 7.70 (2H, m), 7.26–7.15 (5H, m), 6.40 (1H, d, J=15.6 Hz), 6.18 (1H, m), 4.24 (2H, m), 3.28 (1H, dd, J=14.0, 7.3 Hz), 3.00 (1H, dd, J=14.0, 7.3 Hz), 1.92 (3H, s), 1.25 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 172.1, 168.6, 137.2, 134.3, 134.1, 131.7, 128.5, 127.3, 126.2, 124.2, 123.5, 123.2, 63.4, 61.6, 40.0, 22.3, 14.0. MS (FAB^+) m/z: 364 ($M+H^+$, 51), 216 (100). HRMS calcd for $C_{22}H_{22}NO_4$ ($M+H^+$) 364.1549, found 364.1544.

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