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Synthesis of δ-Lactone and Amino Acid Frameworks Utilizing the Umpoled Reactivity of β,γ-Alkenyl α-Iminoester

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Makoto Shimizu

Makoto Shimizu received his PhD from Tokyo Institute of Technology (1981). After a postdoctoral work with Professor B. M. Trost, he became an Assistant Professor of the University of Tokyo (1983), a Senior Research Associate at Riken Institute of Physical and Chemical Research (1984), an Associate Professor of Mie University (1989), and a Full Professor there (1999*)*. Since 2015, he is a dean of the Graduate School of Engineering. His research interests focus on the exploration into new C-C bond forming and/or asymmetric reactions using organometallics and application to the synthesis of new functional materials and bioactive products.

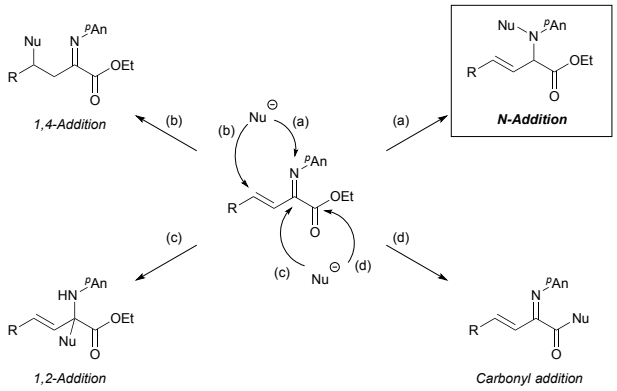
Abstract

An umpolung *N*-alkylation reaction of β,γ-alkenyl α-iminoesters was studied, and various tandem reactions were found utilizing this *N*-alkylation. A useful synthesis of δ-lactones and dienamines was developed by tandem *N*-alkylation/vinylogous aldol-type reaction. The synthesis of α-quaternary alkenyl amino esters was also developed via the tandem *N*-alkylation/bromination/*C*-alkylation. These methods using β,γ-alkenyl α-iminoesters are operationally simple and useful, and exhibit broad substrate generality.

Introduction

α-Imino ester has a unique reactivity due to the structure having an ester part located next to the imino carbon. Since it enables decreasing the LUMO energy of the imino nitrogen, it sometimes shows an unusual type of reaction, an umpolung reaction. Although an umpolung of the α-iminoester is difficult due to the electronegativity of the imino group, it can lead to the introduction of substituents into the nitrogen atom of the amino acid frameworks.[1,2] Our laboratory has developed umpolung reactions of α-imino esters.[3] In 2013, we reported the *N*-alkylation of β,γ-alkynyl α-iminoesters followed by regioselective acylation through the formation of magnesium yne-enolates.[3n] Recently we have reported the *N*,*N*,*C*-trialkylation of *N*-*p*-toluoyloxyiminoesters with three kinds of nucleophiles for construction of trialkylated amino esters.[3q]

In the context to construct a new type of C-C bond formation utilized umpolung *N*-addition to α-iminoester, we focused on the β,γ-alkenyl α-iminoester as a substrate. Since β,γ-alkenyl α-iminoester has an unsaturated olefin moiety which tends to more readily undergo 1,4-addition reaction compared to the alkyne moiety of β,γ-alkynyl α-iminoester, the development of the selective *N*-alkylation is difficult due to undesired side reactions caused by the reaction of the olefin such as 1,4-addition (Scheme 1, b), 1,2-addition (c) and carbonyl addition (d). Herein we report new types of tandem reactions utilizing *N*-alkylation of β,γ-alkenyl-α-iminoester for the syntheses of δ-lactones, dienamines and α-quaternary alkenyl aminoesters.



Scheme 1. Possible reactions to β,γ-alkenyl α-iminoester.

Results and Discussion

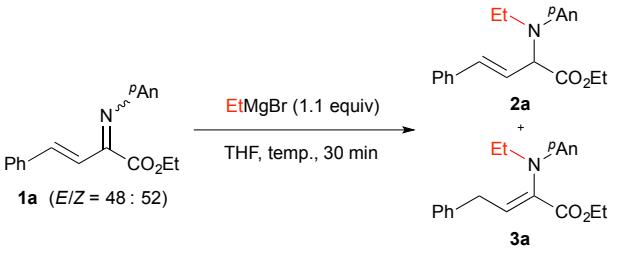
Initially *N*-alkylation reaction of the β,γ-alkenyl α-iminoester **1a** was carried out under the *N*-alkylation conditions optimized for the β,γ-alkynyl α-iminoester (with 1.1 equivs of EtMgBr in THF at −78 °C to rt for 30 min), to give the desired *N*-addition products **2a** and **3a** in 24% combined yield (Table 1, entry 1), in which isomers **2a** and **3a** were likely to be formed by α- or γ-protonation of the magnesium enolate generated by *N*-ethylation at the quenching step. When the reaction was carried out at -78 ^{o}C and -95 ^{o}C, the desired products were obtained in similar yields together with the recovery of the starting material (entries 3 and 4). From these results and the ratio of *E*/*Z* geometric isomers of the starting materials, we assumed that only a single geometric isomer of the starting iminoester participated in the reaction, while the other isomer was inert to the *N*-alkylation.

To verify our hypothesis, various substrates were synthesized, and *N*-alkylation at -78 ^{o}C was carried out, in which the geometry of the substrates was assumed from the computational study (Table 2). As shown in Table 2, a trend was found that as the ratio of the (*E*)-isomer **1** increased, the yields of *N*-alkylation products **2** and **3** were improved. In particular, when the reaction of the substrate having a mesityl group **1e** was carried out, the yield was improved up to 61%, presumably due to the preferred formation of the *E* isomer in the substrate (entry 5). These results indicate that only the (*E*)-isomer participates in the reaction, while the (*Z*)-isomer

does not react but isomerizes to the (*E*)-isomer at room temperature, since the ratio of the diastereomers in the recovered imino ester **1** was same as that in the starting material. Moreover, the computational study supports our hypothesis, in which the ratios of diastereomers are constant at >25 °C.[3o]

To improve the yield of *N*-alkylated product, we focused on suppression of the side reactions to β,γ-alkenyl α-imino ester. When β,γ-alkenyl α-imino ester having a bulky 2,6-dimethyl phenyl group at the terminal alkene was used to suppress a 1,4-addition reaction to conjugate imine and the reaction was carried out at -78 to 40 °C, the desired *N*-alkylation reaction proceeded selectively to provide the *N*-alkylated product **5a** in 85% yield (Table 3, entry 1). Further improvement of the yield was achieved by using diphenyl iminoester **4b**, and the *N*-adduct **5b** was obtained in 92% yield (entry 2) Various substituent patterns including 2-thienyl, 4-MeOC$_6$H$_4$- and 4-FC$_6$H$_4$ group also allowed to give the *N*-addition products **4c-e** in good to high yields (entries 3-5).

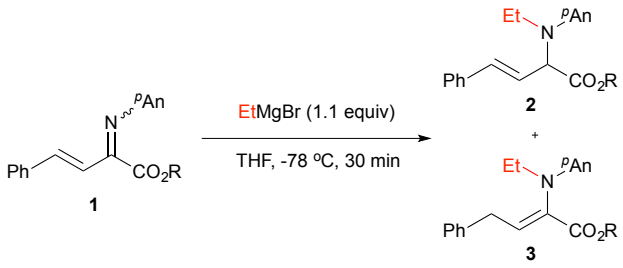
Table 1. Optimization of *N*-alkylation to β,γ-alkenyl α-iminoester.[a]



Entry	T /°C	Yield[b] /%	**2a** : **3a**	RSM[c] /%
1	-78 to rt	24	83 : 17	0
2	-78 to 0	31	71 : 29	0
3	-78	33	67 : 33	50
4	-95	25	76 : 24	66

[a] The reaction was carried out according to the general procedure.
[b] Isolated yield.
[c] Recovery of the starting material.
^{p}An = *p*-MeOC$_6$H$_4$.

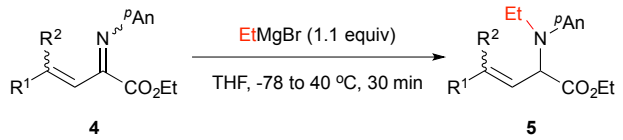
Table 2. *N*-Alkylation at -78 °C for various substrates.[a]



Entry	R	**1** (*E* : *Z*)	Yield[b] /%	**2** : **3**	RSM[c] /% (*E* : *Z*)
1	^{i}Pr	**1b** (33 : 67)	21 (**2b**+**3b**)	67 : 33	47 (33 : 67)
2	Bn	**1c** (40 : 60)	25 (**2c**+**3c**)	68 : 32	50 (40 : 60)
3	Et	**1a** (48 : 52)	33 (**2a**+**3a**)	67 : 33	50 (48 : 52)
4	Me	**1d** (58 : 42)	34 (**2d**+**3d**)	79 : 21	51 (58 : 42)
5	Mes	**1e** (67 : 32)	61 (**3e**)	64 : 36	27 (67 : 32)

[a] The reaction was carried out according to the general procedure.
[b] Isolated yield.
[c] Recovery of the starting material.

Table 3. Scope of substrates.[a]



Entry	R^1	R^2	**4**	Yield[b] /%	
				5	*dr*
1	2,6-Me$_2$C$_6$H$_3$	H	**4a** (*E*/*Z* = 55 : 45)	85 (**5a**)	-
2	Ph	Ph	**4b** (*E*/*Z* = 89 : 11)	92 (**5b**)	-
3	2-thienyl	2-thienyl	**4c** (*dr* = 90 : 10)	83 (**5c**)	-
4	2-thienyl	4-MeOC$_6$H$_4$	**4d** (*dr* = 57 : 21 : 16 : 6)	81 (**5d**)	84 : 16[c]
5	2-thienyl	4-FC$_6$H$_4$	**4e** (*dr* = 84 : 16)	75 (**5e**)	87 : 13[c]

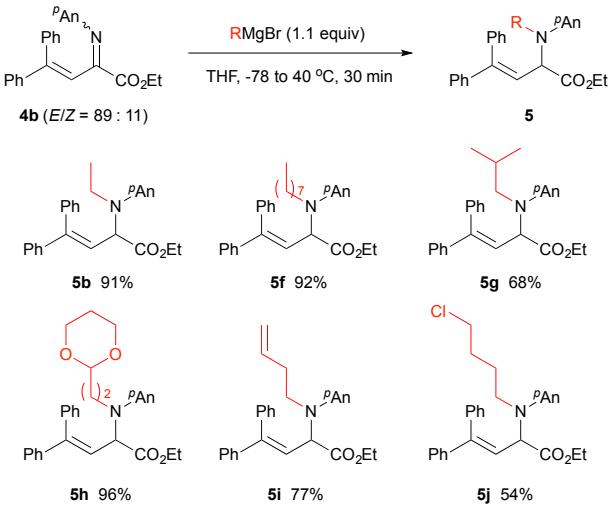
[a] The reaction was carried out according to the general procedure.
[b] Isolated yield.
[c] Olefin geometry of the product was not determined.

Under these optimized conditions, the scope of Grignard reagents was examined (Scheme 2). Linear primary alkyl Grignard reagents provided the desired *N*-adducts **5b**,**f** in excellent yields, while a branched alkyl Grignard reagent afforded the desired product **5g** in good yield. Moreover, Grignard reagents with functional group such as cyclic acetals, terminal alkene, and halogen, were also effective in this reaction (**5h-j**). In most cases nucleophilic addition to the ethoxycarbonyl group occurred as the side reaction, which resulted in low yields of the desired products.

Gratifyingly, we found that when benzaldehyde was used as an electrophile, a tandem *N*-alkylation/vinylogous aldol-type reaction proceeded regioselectively to give the δ-lactone **7a** in 77% yield together with the *N*-alkylated product **5b** in 22% yield (Table 4, entry 1). Aldol reactions using the enolates prepared via the 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds are useful in organic synthesis to promote three-component coupling reactions, which can build complex molecules.[4] The vinylogous aldol-type reactions[5] reported so far used allenic esters as the starting materials.[6d] The directed vinylogous aldol-type reaction[6] using the enolate prepared in situ is effective in terms of the atom economy as compared to the Mukaiyama vinylogous aldol-type reaction,[7] although its regioselectivity[6e,f] was affected by steric factors of the substrates, and it was required to use excess amounts of bulky Lewis acids.[6a,b,g] α-Amino-δ-lactones are important precursors to biologically active compounds such as pyrano[3,4-b]indol-1(9H)-ones known as an anticancer agent.[8] Therefore, we next investigated the tandem *N*-alkylation/vinylogous aldol-type reaction in the presence of an electrophile, and after various examinations of vinylogous aldol-type reaction conditions, the optimized reaction conditions were found to be use of 5.0 equivalents of aldehyde at reflux for 1.5 h. On the other hand, although the *N*-alkylation followed by hydrolysis of the resulting enamine provided a simple *N*-alkylated product as a byproduct, we hypothesized the retro-aldol reaction of the aldol product via α-addition might occur to provide this *N*-alkylated product. Thus, we examined the ester moiety of the substrates, the addition of a Lewis acid to increase aldehyde reactivity, and the effect of a Lewis base on the retro-aldol reaction in order to increase the γ-adduct. However, the yield of δ-lactone **7a** did not increase (entries 2-6). We cannot completely rule out our hypothesis because these results suggest that the magnesium α-aldolate may be stabilized by a strong chelation between the magnesium and the nitrogen atoms.

Then the scope of substrates, Grignard reagents, and aldehydes was examined under the optimized reaction conditions (Scheme 3). The use of primary Grignard reagents such as isobutyl, homoallyl, chlorobutyl, and 1,3-dioxanylethyl promoted the *N*-alkylation reaction followed by cyclization to give the desired δ-lactones in moderate to good yields (**7b-e**). Aromatic and heteroaromatic aldehydes afforded the desired products **7f-h** in moderate to high yields. An α,β-unsaturated aldehyde, cinnamaldehyde, gave the product **7i** in 79% yield.

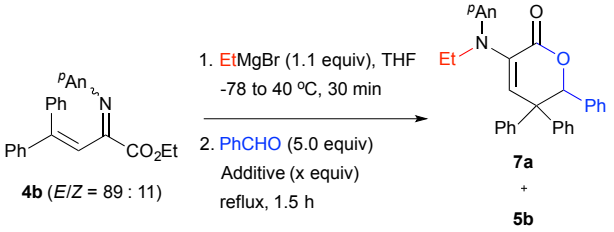
A proposed reaction mechanism is shown in Scheme 4. After isomerization of the *Z*-**4** isomer to the more reactive *E*-isomer **4** at room temperature, *N*-alkylation of Grignard reagent proceeds to form the enolate intermediate **A**, which is protonated at the γ-position to provide the product **6**, while protonation at the α-position leads to the product **5**. On the other hand, the vinylogous aldol-type reaction of the enolate intermediate **A** with aldehydes followed by the cyclization leads to the lactone **7** via the intermediate **B**, while addition to aldehyde at the α-position forms the product **C** which would give back to the **5** via retro-aldol reaction.



[a] The reaction was carried out according to the general procedure.
[b] Yields refer to pure isolated compounds.

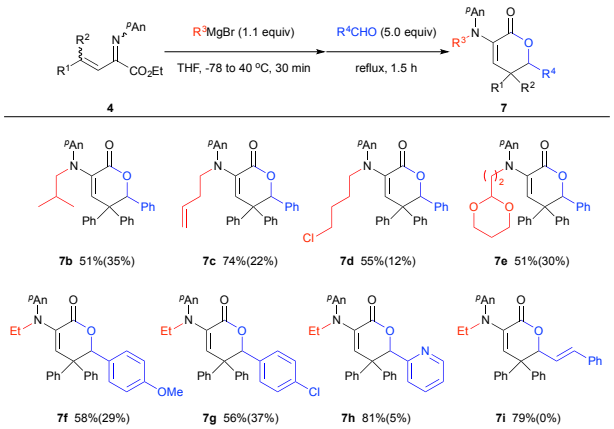
Scheme 2. Scope of Grignard reagents for *N*-alkylation.[a,b]

Table 4. *N*-Alkylation at -78 °C for various substrates.[a]



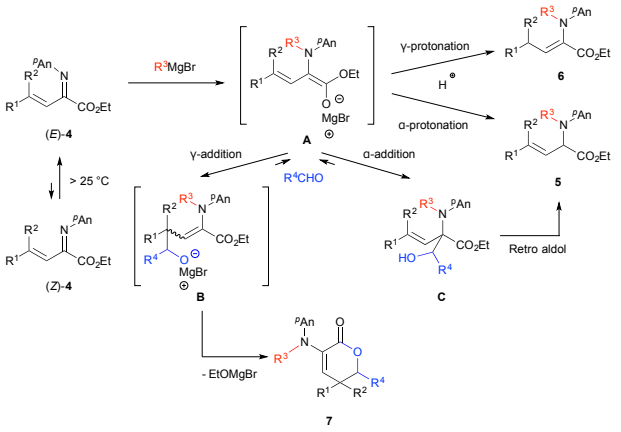
Entry	Additive /x eq	Yield[b] /%	
		7a	**5b**
1	None	77	22
2[c]	$BF_3 \cdot OEt_2$ /5.0	0	25
3[c]	$Ti(OiPr)_4$ /5.0	15	68
4[d]	DMSO /1.0	40	29
5[e]	DMSO /1.0	47	32
6[e]	Et_3N /1.0	72	26

[a] The reaction was carried out according to the general procedure.
[b] Isolated yield.
[c] A mixture of the aldehyde and the additive was added.
[d] The additive was added before the addition of the aldehyde.
[e] The additive was added after the addition of the aldehyde.



[a] The reaction was carried out according to the general procedure.
[b] Yields refer to pure isolated compounds, and yields of *N*-adduct are in the parentheses.

Scheme 3. Tandem *N*-alkylation/vinylogous aldol-type reaction.[a,b]



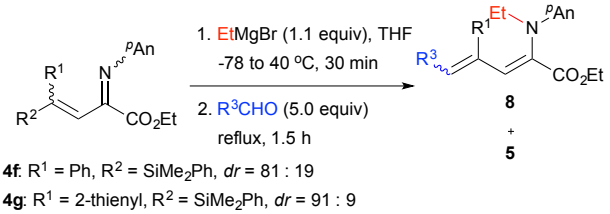
Scheme 4. Proposed reaction mechanism.

Furthermore a tandem reaction of β,γ-alkenyl α-iminoester having a silyl group at the terminal alkene moiety was investigated, and the results are shown in Table 5. Interestingly, Peterson olefination rather than intramolecular cyclization proceeded after the vinylogous aldol-type reaction to afford the dienamines **8** in moderated yields (entries 1 and 2). The use of cinnamaldehyde provided the trienamine product in 71% yield (entry 3). The geometry of these products prefers to be trans form caused by the *syn*-elimination of the silanolate on the basic Perterson olefination.

Since the tandem *N*-alkylation/vinylogous aldol-type reaction starting from β,γ-alkenyl α-iminoester was developed utilizing γ-addition of the magnesium dienolate, we next focused on the selective α-addition of dienolate to synthesize the α quaternary alkenyl amino acid derivatives. Quaternary α-amino acids are an interesting class of nonproteinogenic acids and also powerful enzyme inhibitors,[9] and β,γ-alkenyl α-iminoesters are known as an important α-amino acid frameworks for the bioactive compounds widely existing in the natural compounds.[10] It is highly required to synthesize the compounds that can introduce various nucleophiles freely on the imino nitrogen. As α-adducts were not obtained presumably due to the retro-aldol reaction when aldehydes were used as mentioned above, various types of electrophiles were examined such as iodomethane, allyl bromide and acetyl chloride for the tandem *N*-alkylation/α-addition reaction as shown in Scheme 5. However the desired α-adducts were not obtained at all.

We next examined a further alternative synthesis of α-quatenary alkenyl amino esters utilizing a sequential *N*-alkylation/oxidation/nucleophilic addition to β,γ-alkenyl-α-imino ester **4b**. As an initial reaction, the iminoester **4b** first reacted with 1.2 equivs of EtMgBr in THF at -78 to 40 °C for 30 min followed by bromination with 1.2 equivs of NBS at 0 °C for 15 min and treatment with another 1.2 equivs of EtMgBr at 0 °C for 15 min. The desired product **9a** was obtained in 32% yield (Table 6, entry 1). A series of reaction conditions including the amount of oxidants and second nucleophiles were examined in detail, and the results are summarized in Table 6. Regarding the amounts of oxidants (entries 1-3), it was found that the use of 1.5 equivs of NBS was the most efficient to give the desired product **9a** in 68% yield (entry 2). Other oxidants such as NCS, NIS, DBDMH and BPO also provided the products in moderate to good yields (entries 4-7). Examination of the second nucleophile showed that the desired product **9** was obtained in a maximum 90% yield when 2.0 equivs of EtZnI were used at 0 °C to room temperature for 1 h (entry 12).

Table 5. Tandem reaction of β,γ-alkenyl α-iminoesters bearing a silyl group.[a]

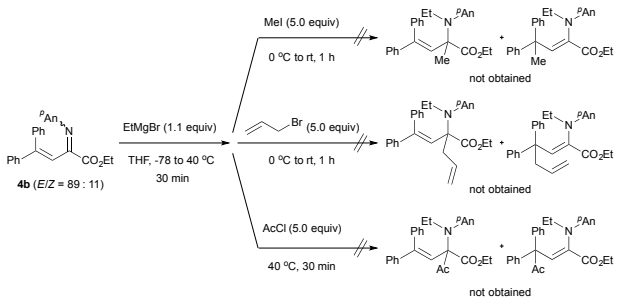


4f: R^1 = Ph, R^2 = $SiMe_2Ph$, *dr* = 81 : 19

4g: R^1 = 2-thienyl, R^2 = $SiMe_2Ph$, *dr* = 91 : 9

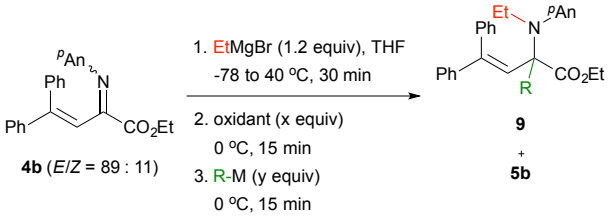
Entry	4	R^3	Yield[b]/%		
			8	*dr*	**5**
1	**4f**	Ph	61 (**8a**)	87:13	14 (**5q**)
2	**4g**	Ph	49 (**8b**)	93:7	4 (**5r**)
3	**4f**	(*E*)-PhCH=CH	71 (**8c**)	64:36	trace

[a] The reaction was carried out according to the general procedure.
[b] Isolated yield.



Scheme 5. Tandem *N*-alkylation/electrophilic addition reactions.

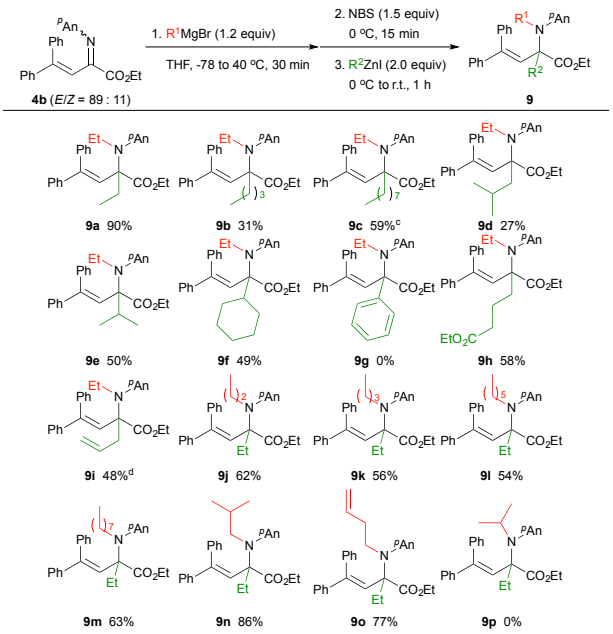
Table 6. Optimization of tandem *N*-alkylation/oxidation/1,2-addition.[a]



4b (*E*/*Z* = 89 : 11)

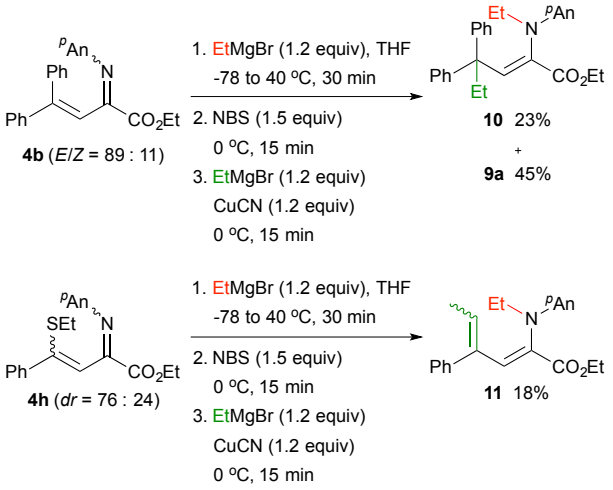
Entry	Oxidant/x eq	R-M/y eq	Yield[b]/%	
			9	**5b**
1	NBS/1.2	EtMgBr/1.2	32 (**9a**)	39
2	NBS/1.5	EtMgBr/1.2	68 (**9a**)	5
3	NBS/2.0	EtMgBr/1.2	52 (**9a**)	10
4	NCS/1.5	EtMgBr/1.2	66 (**9a**)	4
5	NIS/1.5	EtMgBr/1.2	56 (**9a**)	10
6	DBDMH/0.75	EtMgBr/1.2	61 (**9a**)	9
7	BPO/1.5	EtMgBr/1.2	57 (**9a**)	0
8	NBS/1.5	Et_2Zn/1.2	48 (**9a**)	43
9	NBS/1.5	Et_2AlCl/1.2	20 (**9a**)	42
10	NBS/1.5	^{n}BuLi/1.2	0 (**9b**)	0
11[c]	NBS/1.5	EtZnI/1.2	80 (**9a**)	0
12[c]	NBS/1.5	EtZnI/1.2	90 (**9a**)	0

[a] The reaction was carried out according to the general procedure.
[b] Isolated yield.
[c] Reaction was carried out at 0 °C to rt for 1 h.
DBDMH = 1,3-dibromo-5,5-dimethylhydantoin.



[a] The reaction was carried out according to the general procedure.
[b] Yields refer to pure isolated compounds.
[c] ^{n}OctMgBr was used instead of Zn reagent.
[d] Tetraallyltin was used instead of Zn reagent.

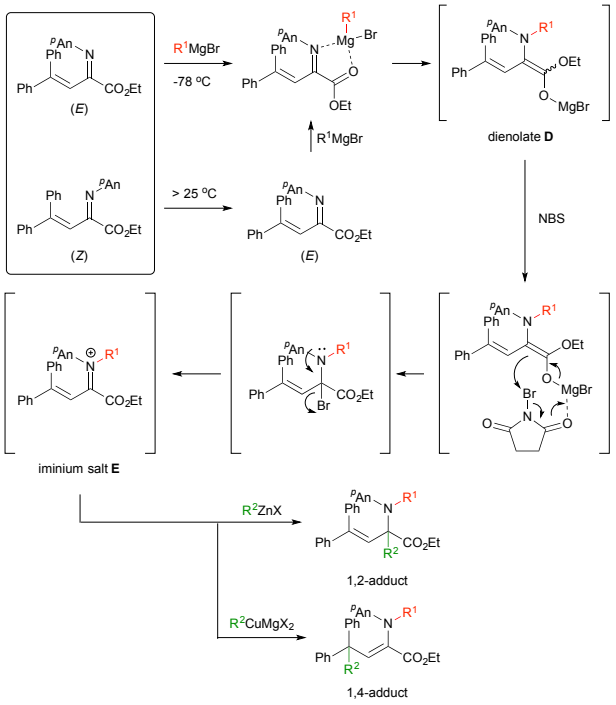
Scheme 6. Scope of first and second nucleophiles.[a,b]



Scheme 7. Tandem *N*-alkylation/oxidation/1,4-addition reaction.

Regarding the sope of second nucleophiles, organozinc reagents was evaluated under the optimized conditions (Scheme 6). In the case of the bulky substituents such as isopropyl and the cyclohexyl group, the desired products **9e** and **9f** were obtained in moderate yields, while the introduction of butyl and isobutyl groups decreased the yield (**9b**,**d**). Aromatic zinc reagents did not appear to be effective in this reaction (**9g**). The use of the zinc reagent having a functional group allowed the desired product in good yield (**9h**). On the other hand, the use of *n*-octyl Grignard reagent and tetraallyltin was also effective in this reaction to afford the desired product **9c** and **9i** in moderate yields.

Use of the Grignard reagent as a first nucleophile was next examined. Primary alkyl Grignard reagents (Et, ^{n}Pr, ^{n}Bu, ^{n}Hex, ^{n}Oct, and ^{i}Bu groups) gave the desired products **9j-n** in good to high yields. When homoallyl Grignard reagent was used, the corresponding product **9o** was also obtained in good yield. Secondary alkyl Grignard reagent (isopropyl group) did not afford the *N*-alkylated product **9p** at all presumably due to the steric hindrance.



Scheme 8 Plausible mechanism.

Regioselective 1,4-addition reaction for the iminium salt[11] formed in situ was next investigated (Scheme 7). The use of organocopper reagent for the second nucleophile gave the desired 1,4-adduct **10** in 23% yield. It was also found that when the β,γ-alkenyl α-iminoester **4h** having an ethylthio group at the terminal alkene was used as the substrate, the enamine product **11** was obtained in 18% yield via the 1,4-addition for iminium salt followed by the elimination of ethylthio group albeit in low yield.

A proposed reaction mechanism is shown in Scheme 8. The inert (*Z*)-iminoester isomerizes into its reactive (*E*)-iminoester by heating above room temperature. The *N*-alkylation proceeds with the Grignard reagent to give the magnesium dienolate **D** through formation of a five-membered intermediate composed of the imino nitrogen, the carbonyl oxygen, and the magnesium atom. The enolate **D** is brominated with NBS to give an iminium salt as the intermediate **E**, which reacts with the second nucleophile to give the alkenyl amino ester and the enamined through 1,2-addition or 1,4-addition respectively.

Conclusion

We have developed a one-pot synthesis of δ-lactones and dienamines using umpolung *N*-alkylation of β,γ-alkenyl α-iminoester followed by vinylogous aldol-type reaction. This method shows a unique reactivity for the cyclization or Peterson olefination in good to high yields. Moreover, we also show the synthesis of α-quaternary alkenyl aminoesters utilizing a β,γ-alkenyl α-iminoester via an intermediary iminium salt formed by the bromination of the aminoester enolate in high yields.

Experimental

General Aspects. Infrared spectra were determined on a JASCO FT/ IR-460 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL ECX-400P JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. Tetrahydrofuran (THF) was distilled from benzophenone ketyl immediately before use. Purification of products was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254). β,γ-Alkenyl α-iminoesters **1a-e, 4a-h** were prepared according to the reported procedure and characterization data of compounds **1**-**8** has already been reported.[3o]

General procedure for the *N*-alkylation to β,γ-alkenyl iminoester (Table 1, 2 and 3, Scheme 2). Under an argon atmosphere, a suspension of β,γ-Alkenyl α-iminoester **1** or **4** (0.15 mmol) in THF (2.0 mL) was stirred at -78 ^{o}C for 5 min, and to it was added Grignard reagent in THF solution (1.1 equiv) slowly. After 5 min, the mixture was warmed to 40 ^{o}C immediately and was stirred for 25 min. The reaction was quenched with sat. $NaHCO_3$ aq. (3.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (n-hexane/ethyl acetate = 5 / 1) to give the desired compounds **2**, **3**, and **5**.

General procedure for the tandem *N*-alkylation/vinylgous aldol-type reaction (Table 4, Scheme 3). Under an argon atmosphere, a suspension of β,γ-Alkenyl α-iminoester **4** (0.10 mmol) in THF (2.0 mL) was stirred at -78 ^{o}C for 5 min, and to it was added Grignard reagent in THF solution (1.1 equiv). After stirring for 5 min at -78 ^{o}C, the mixture was warmed to 40 ^{o}C immediately and stirred for 25 min. After the consumption of substrate was confirmed by TLC, the reaction mixture was heated to reflux and to it was added an aldehyde (5.0 equiv) and was stirred for 1.5 h. The reaction was quenched with sat. $NaHCO_3$ aq. (3.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 5 / 1) to give the desired compounds **7** and **5**.

General procedure for the tandem *N*-alkylation/γ-addition/peterson olefination (Table 5). Under an argon atmosphere, a suspension of β,γ-Alkenyl α-iminoester **4** (0.10 mmol) in THF (2.0 mL) was stirred at -78 ^{o}C for 5 min, and to it was added EtMgBr in THF solution (1.1 equiv). After stirring for 5 min at -78 ^{o}C, the mixture was warmed to 40 ^{o}C immediately and stirred for 25 min. After the consumption of substrate was confirmed by TLC, the mixture was heated to reflux and to it was added an aldehyde (5.0 equiv), and was stirred for 1.5 h. The reaction was quenched with sat. $NaHCO_3$ aq. (3.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 9 / 1) to give the desired compounds **8** and **5**.

General procedure for the tandem *N*-alkylation/bromination/1,2-addition (Table 6, Scheme 6). Under an argon atmosphere, a suspension of β,γ-Alkenyl α-iminoester **4** (0.10 mmol) in THF (2.0 mL) was stirred at -78 ^{o}C for 5 min, and to it was added Grignard reagent in THF solution (1.1 equiv). After stirring for 5 min at -78 ^{o}C, the mixture was warmed to 40 ^{o}C immediately and stirred for 20 min. After the consumption of the substrate was confirmed by TLC, the mixture was cooled to 0 ^{o}C and stirred for 5 min and to it was added NBS (1.5 equiv). After stirring for 15 min, to it was added RZnI in THF solution (2.0 equiv), which was prepared according to the literature,[12] slowly and the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. $NaHCO_3$ aq. (3.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 10 / 1) to give the desired compound **9**.

Ethyl 2-ethyl-2-[ethyl(4-methoxyphenyl)amino]-4,4-diphenylbut-3-enoate (9a). Yield 90%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (dd, *J* = 7.1, 7.1 Hz, 3H), 0.95 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.14 (dd, *J* = 7.3, 7.3 Hz, 3H), 1.67-1.80 (m, 2H), 2.92 (dq, *J* = 7.2, 13.6 Hz, 1H), 3.24 (dq, *J* = 7.2, 13.6 Hz, 1H), 3.73-3.93 (m, 5H including singlet at 3.75 ppm, 3H), 6.61 (s, 1H), 6.70-6.80 (m, 4H), 7.06-7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 14.1, 14.7, 30.7, 44.3, 55.3, 60.4, 70.3, 113.3, 126.9, 127.0, 127.2, 127.5, 127.6, 128.0, 129.7, 131.2, 139.5, 139.6, 141.5, 143.7, 155.8, 173.6; IR(neat) 2975, 1722, 1509, 1463, 1443, 1377, 1284, 1245, 1220, 1118, 1074, 1037, 832, 760, 701 cm^{-1}; HRMS(EI):Calcd for $C_{29}H_{33}NO_3(M)^+$ 443.2460, found 443.2455.

Ethyl 2-(2,2-diphenylvinyl)-2-[ethyl(4-methoxyphenyl)amino]hexanoate (9b). Yield 31%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.9 Hz, 3H), 0.86 (dd, *J* = 6.7, 6.7 Hz, 3H), 1.13 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.19-1.29 (m, 3H), 1.59 (dt, *J* = 6.9, 15.1 Hz, 1H), 1.67-1.79 (m, 2H), 2.92 (dq, *J* = 6.7, 14.0 Hz, 1H), 3.24 (dq, *J* = 6.7, 14.0 Hz, 1H), 3.66-3.79 (m, 4H, including singlet at 3.74 ppm, 3H), 3.87 (dq, *J* = 7.1, 10.8 Hz, 1H), 6.63 (s, 1H), 6.72-6.79 (m, 4H), 7.06-7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.7, 23.2, 26.5, 37.6, 44.2, 55.2, 60.3, 69.8, 113.2, 126.9, 127.0, 127.2, 127.4, 127.5, 128.0, 129.7, 131.6, 139.5, 139.6, 141.2, 143.6, 155.7, 173.5; IR(neat) 2959, 2931, 1722, 1507, 1465, 1443, 1377, 1282, 1244, 1181, 1125, 1074, 1035, 759, 701 cm^{-1}; HRMS(EI): Calcd for $C_{31}H_{37}NO_3(M)^+$ 471.2773, found 471.2780.

Ethyl 2-(2,2-diphenylvinyl)-2-[ethyl(4-methoxyphenyl)amino]decanoate (9c). Yield 59%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.8 Hz, 3H), 0.86 (dd, *J* = 7.0, 6.8 Hz, 3H), 1.12-1.27 (m, 15H, including dd at 1.13 ppm, *J* = 7.2, 7.3 Hz, 3H), 1.58-1.69 (m, 2H), 2.91 (dq, *J* = 6.8, 13.8 Hz, 1H), 3.23 (dq, *J* = 7.0, 13.8 Hz, 1H), 3.72-3.80 (m, 4H, including singlet at 3.76 ppm, 3H), 3.88 (dq, *J* =7.2, 10.8 Hz, 1H), 6.62 (s, 1H), 6.72-6.78 (m, 4H), 7.05-7.07 (m, 2H), 7.15-7.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.7, 22.6, 24.4, 29.3, 29.5, 30.1, 31.8, 37.9, 44.2, 55.3, 60.4, 69.9, 113.3, 126.9, 127.0, 127.2, 127.4, 127.6, 127.8, 128.0, 129.8, 131.7, 139.5, 139.6, 141.2, 143.7, 155.7, 173.6; IR(neat) 3055, 2927, 2856, 1723, 1509, 1445, 1375, 1285, 1243, 1180, 1125, 1074, 1037, 762, 700 cm^{-1}; HRMS(EI): Calcd for $C_{35}H_{45}NO_3(M)^+$ 527.3399, found 527.3422.

Ethyl 2-(2,2-diphenylvinyl)-2-[ethyl(4-methoxyphenyl)amino]-4-methylpentanoate (9d). Yield 27%; Red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (dd, *J* = 6.9, 6.9 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 1.17 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.56 (dd, *J* = 6.4, 13.7 Hz, 1H), 1.76 (dd, *J* = 6.4, 13.7 Hz, 1H),

1.86-2.01 (m, 1H), 2.85 (dq, *J* = 6.9, 13.3 Hz, 1H), 3.18 (dq, *J* = 6.9, 13.3 Hz, 1H), 3.76 (s, 3H), 3.82 (dq, *J* = 7.2, 11.0 Hz, 1H), 3.92 (dq, *J* = 7.2, 11.0 Hz, 1H), 6.71 (s, 3H), 6.73 (s, 1H), 7.10-7.35 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.3, 23.7, 24.3, 25.0, 44.0, 46.3, 55.3, 60.4, 69.4, 113.1, 126.8, 127.0, 127.2, 127.5, 128.0, 128.1, 129.8, 131.4, 139.3, 139.7, 141.3, 143.8, 155.8, 173.8; IR(neat) 2957, 2868, 1719, 1508, 1465, 1443, 1385, 1289, 1244, 1214, 1181, 1128, 1035, 758, 701 cm^{-1}; HRMS(EI): Calcd for $C_{31}H_{37}NO_3(M)^+$ 471.2773, found 471.2778.

Ethyl 2-[ethyl(4-methoxyphenyl)amino]-2-isopropyl-4,4-diphenylbut-3-enoate (9e). Yield 50%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (dd, *J* = 7.0, 7.0 Hz, 3H), 1.08-1.16 (m, 9H), 2.39 (sep, *J* = 6.7 Hz, 1H), 2.86 (dq, *J* = 7.0, 13.1 Hz, 1H), 3.10 (dq, *J* = 7.0, 13.1 Hz, 1H), 3.20 (dq, *J* = 7.2, 10.5 Hz, 1H), 3.67 (dq, *J* = 7.2, 10.5 Hz, 1H), 3.80 (s, 3H), 5.98 (s, 1H), 6.79-6.82 (m, 2H), 6.86-6.88 (m, 2H), 7.05-7.07 (m, 2H), 7.15-7.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.7, 19.2, 20.4, 34.5, 45.4, 55.4, 60.0, 73.8, 113.3, 126.7, 126.8, 127.4, 127.4, 127.9, 128.8, 129.8, 130.2, 139.6, 140.4, 140.9, 145.0, 156.4, 173.0; IR(neat) 2966, 2931, 1719, 1684, 1652, 1558, 1540, 1507, 1457, 1383, 1242, 1035, 842, 763, 701 cm^{-1}; HRMS(EI): Calcd for $C_{30}H_{35}NO_3(M)^+$ 457.2617, found 457.2630.

Ethyl 2-cyclohexyl-2-[ethyl(4-methoxyphenyl)amino]-4,4-diphenylbut-3-enoate (9f). Yield 49%; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (dd, *J* = 6.8, 6.8 Hz, 3H), 1.09-1.28 (m, 8H, including doublet at 1.11 ppm, *J* = 7.0, 7.0 Hz, 3H), 1.62-1.65 (m, 1H), 1.73-1.78 (m, 2H), 1.99-2.03 (m, 1H), 2.10-2.12 (m, 1H), 2.29-2.33 (m, 1H), 2.85 (dq, *J* = 6.8, 13.3 Hz, 1H), 3.04 (dq, *J* = 6.8, 13.3 Hz, 1H), 3.13-3.22 (m, 1H), 3.72 (dq, *J* = 7.0, 10.7 Hz, 1H), 3.80 (s, 3H), 5.98 (s, 1H), 6.79-6.85 (m, 4H), 7.05-7.33 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.5, 26.7, 27.0, 27.2, 28.9, 31.0, 44.9, 45.0, 55.4, 60.0, 73.6, 113.2, 126.7, 126.8, 127.4, 127.9, 129.5, 129.8, 130.2, 139.7, 140.2, 140.3, 145.0, 156.3, 173.0; IR(neat) 2926, 2853, 1721, 1509, 1445, 1241, 1213, 1179, 1036, 835, 756, 700 cm^{-1}; HRMS(EI): Calcd for $C_{33}H_{39}NO_3(M)^+$ 497.2930, found 497.2933.

Diethyl 2-(2,2-diphenylvinyl)-2-[ethyl(4-methoxyphenyl)amino]hexanedioate (9h). Yield 58%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 7.0, 7.0 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.21 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.60-1.76 (m, 3H), 1.91-2.04 (m, 1H), 2.16 (t, *J* = 7.1 Hz, 2H), 2.95 (dq, *J* = 7.0, 13.6 Hz, 1H), 3.30 (dq, *J* = 7.0, 13.6 Hz, 1H), 3.67 (dq, *J* = 7.2, 10.9 Hz, 1H), 3.77 (s, 3H), 3.80 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 6.47 (s, 1H), 6.73-6.77 (m, 2H), 6.84-6.87 (m, 2H), 7.09-7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 15.0, 19.9, 34.7, 37.0, 45.1, 55.3, 60.2, 60.4, 69.7, 113.4, 127.0, 127.2, 127.2, 127.6, 128.0, 128.8, 129.9, 131.3, 139.3, 139.5, 141.8, 143.5, 156.5, 173.0, 173.4; IR(neat) 2977, 2935, 1728, 1508, 1464, 1443, 1374, 1288, 1245, 1181, 1094, 1035, 834, 758, 702 cm^{-1}; HRMS(EI): Calcd for $C_{33}H_{39}NO_5(M)^+$ 529.2828, found 529.2814.

Ethyl 2-(2,2-diphenylvinyl)-2-[ethyl(4-methoxyphenyl)amino]pent-4-enoate (9i). Yield 48%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (dd, *J* = 6.9, 6.9 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 2.44 (dd, *J* = 7.7, 14.1 Hz, 1H), 2.55 (dd, *J* = 6.3, 14.1 Hz, 1H), 2.97 (dq, *J* = 6.9, 13.4 Hz, 1H), 3.29 (dq, *J* = 6.9, 13.4 Hz, 1H), 3.71 (dq, *J* = 7.1, 10.8 Hz, 1H), 3.76 (s, 3H), 3.80 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.99-5.07 (m, 2H), 5.96 (dddd, *J* = 6.3, 7.7, 10.9, 18.1, 1H), 6.49 (s, 1H), 6.73-6.75 (m, 2H), 6.83-6.85 (m, 2H), 7.09-7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.8, 42.4, 44.7, 55.3, 60.4, 69.8, 113.3, 117.8, 127.0, 127.1, 127.2, 127.6, 128.0, 128.5, 129.8, 131.5, 134.1, 139.3, 141.7, 143.6, 156.3, 172.9; IR(neat) 3443, 2975, 2360, 1722, 1643, 1507, 1443, 1375, 1286, 1243, 1119, 1034, 833, 757, 700, 576 cm^{-1}; HRMS(EI): Calcd for $C_{30}H_{33}NO_3(M)^+$ 455.2460, found 455.2471.

Ethyl 2-ethyl-2-[(4-methoxyphenyl)(propyl)amino]-4,4-diphenylbut-3-enoate (9j). Yield 62%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (dd, *J* = 7.5, 7.6 Hz, 3H), 0.99 (dd, *J* = 7.1, 7.3 Hz, 3H), 1.12 (dd, *J* = 7.2, 7.3 Hz, 3H), 1.12-1.29 (m, 2H), 1.66-1.80 (m, 2H), 2.88 (dq, *J* = 7.1, 7.4 Hz, 1H), 3.14 (dq, *J* = 7.1, 7.4 Hz, 1H), 3.66 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.74-3.83 (m, 4H including singlet at 3.76 ppm, 3H), 6.50 (s, 1H), 6.72-6.76 (m, 2H), 6.84-6.88 (m, 2H), 7.06-7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 11.6, 14.0, 22.3, 30.5, 52.7, 55.3, 60.2, 70.1, 113.3, 126.9, 127.0, 127.2, 127.6, 128.0, 128.2, 129.8, 131.7, 139.4, 140.1, 141.3, 143.7, 156.2, 173.4; IR(neat) 2960, 2872, 1722, 1508, 1463, 1443, 1286, 1245, 1220, 1181, 1106, 1074, 1037, 758, 700 cm^{-1}; HRMS(EI): Calcd for $C_{30}H_{35}NO_3(M)^+$ 457.2617, found 457.2607.

Ethyl 2-[butyl(4-methoxyphenyl)amino]-2-ethyl-4,4-diphenylbut-3-enoate (9k). Yield 56%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 1.12 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.16-1.40 (m, 4H), 1.73 (q, *J* = 7.3 Hz, 2H), 2.89 (dt, *J* = 6.8, 13.5 Hz, 1H), 3.15-3.22 (m, 1H), 3.68 (dq, *J* = 7.1, 11.0 Hz, 1H), 3.72-3.83 (m, 4H including singlet at 3.75 ppm, 3H), 6.51 (s, 1H), 6.71-6.76 (m, 2H), 6.83-6.87 (m, 2H), 7.07-7.09 (m, 2H), 7.15-7.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 14.0, 14.1, 20.3, 30.5, 31.4, 50.6, 55.3, 60.2, 70.1, 113.3, 126.9, 127.0, 127.2, 127.5, 128.0, 128.0, 129.8, 131.6, 139.4, 140.1, 141.3, 143.7, 156.1, 173.3; IR(neat) 2957, 2933, 1723, 1509, 1464, 1443, 1288, 1245, 1217, 1181, 1115, 1038, 758, 701 cm^{-1}; HRMS (EI): Calcd for $C_{31}H_{37}NO_3(M)^+$ 471.2773, found 471.2756.

Ethyl 2-ethyl-2-[hexyl(4-methoxyphenyl)amino]-4,4-diphenylbut-3-enoate (9l). Yield 54%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.12 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.19-1.36 (m, 8H), 1.73 (q, *J* = 7.4 Hz, 2H), 2.85-2.92 (m, 1H), 3.13-3.20 (m, 1H), 3.68 (dq, *J* = 7.2, 10.8 Hz, 1H), 3.74-3.84 (m, 4H, including singlet at 3.76 ppm, 3H), 6.51 (s, 1H), 6.70-6.76 (m, 2H), 6.82-6.87 (m, 2H), 7.06-7.09 (m, 2H), 7.15-7.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 14.0, 22.7, 26.9, 29.2, 30.5, 31.8, 50.8, 55.3, 60.3, 70.2, 113.3, 126.9, 127.0, 127.2, 127.6, 128.0, 129.8, 131.6, 139.4, 140.1, 141.3, 143.8, 156.1, 173.4; IR(neat) 2955, 2930, 2856, 1723, 1508, 1465, 1443, 1288, 1245, 1181, 1115, 1038, 758, 700 cm^{-1}; HRMS (EI): Calcd for $C_{33}H_{41}NO_3(M)^+$ 499.3086, found 499.3065.

Ethyl 2-ethyl-2-[(4-methoxyphenyl)(octyl)amino]-4,4-diphenylbut-3-enoate (9m). Yield 63%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 6.8, 6.8 Hz, 3H), 0.98 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.12 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.13-1.28 (m, 12H), 1.73 (dq, *J* = 7.4, 14.7 Hz, 2H), 2.88 (dq, *J* = 6.8, 6.9 Hz, 1H), 3.17 (dq, *J* = 6.8, 6.9 Hz, 1H), 3.68 (dq, *J* = 7.1, 11.0 Hz, 1H), 3.73-3.84 (m, 4H, including singlet at 3.76 ppm, 3H), 6.52 (s, 1H), 6.72-6.76 (m, 2H), 6.82-6.87 (m, 2H), 7.06-7.09 (m, 2H), 7.15-7.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 14.0, 14.1, 22.6, 27.2, 29.2, 29.3, 29.5, 30.5, 31.8, 50.8, 55.3, 60.2, 70.2, 113.3, 126.9, 127.0, 127.2, 127.6, 127.8, 128.0, 129.8, 131.6, 139.4, 140.1, 141.3, 143.8, 156.1, 173.4; IR(neat) 2955, 2927, 2854, 1723, 1509, 1464, 1443, 1245, 1221, 1181, 1115, 1038, 760, 701 cm^{-1}; HRMS (EI): Calcd for $C_{35}H_{45}NO_3(M)^+$ 527.3399, found 527.3403.

Ethyl 2-ethyl-2-[isobutyl(4-methoxyphenyl)amino]-4,4-diphenylbut-3-enoate (9n). Yield 86%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.4 Hz, 3H), 1.05-1.08 (m, 9H), 1.33-1.43 (m, 1H), 1.61 (dq, *J* = 7.2, 14.4 Hz, 1H), 1.79 (dq, *J* = 7.2, 14.4 Hz, 1H), 2.93 (dd, *J* = 4.8, 13.0 Hz, 1H), 3.02 (dd, *J* = 9.4, 13.0 Hz, 1H), 3.45 (dq, *J* = 7.2, 10.9 Hz, 1H), 3.58 (dq, *J* = 7.2, 10.9 Hz, 1H), 3.77 (s, 3H), 6.26 (s, 1H), 6.75- 6.79 (m, 2H), 7.03-7.07 (m, 2H), 7.11-7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 13.9, 20.6, 20.8, 27.0, 29.9, 55.3, 60.0, 60.4, 70.0, 113.5, 127.0, 127.1, 127.6, 128.1, 130.2, 130.3, 132.7, 139.0, 140.3, 140.9, 143.7, 157.3, 172.7; IR(neat) 2953, 2867, 1722, 1508, 1465, 1443, 1246, 1222, 1180, 1108, 1093, 1038, 836, 758, 701 cm^{-1}; HRMS (EI): Calcd for $C_{31}H_{37}NO_3(M)^+$ 471.2773, found 471.2775.

Ethyl 2-[but-3-en-1-yl(4-methoxyphenyl)amino]-2-ethyl-4,4-diphenylbut-3-enoate (9o). Yield 77%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.3 Hz, 3H), 1.12 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.67-1.81 (m, 2H), 1.99 (q, *J* = 7.3 Hz, 2H), 2.98 (dt, *J* = 7.4, 13.8 Hz, 1H), 3.30 (dt, *J* = 7.4, 13.8 Hz, 1H), 3.65 (dq, *J* = 7.1, 11.0 Hz, 1H), 3.71-3.82 (m, 4H, including singlet at 3.76 ppm, 3H), 4.97-5.01 (m, 2H), 5.79-5.89 (m, 1H), 6.50 (s, 1H), 6.73-6.77 (m, 2H), 6.84-6.88 (m, 2H), 7.06- 7.08 (m, 2H), 7.15-7.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 14.0, 30.6, 33.6, 50.5, 55.3, 60.3, 70.1, 113.4, 115.4, 127.0, 127.1, 127.2, 127.6, 128.0, 129.8, 131.5, 137.0, 139.3, 139.7, 141.4, 143.6, 156.2, 173.3; IR(neat) 3056, 2976, 2834, 1722, 1508, 1443, 1288, 1246, 1181, 1117, 1075, 1036, 914, 758, 701 cm^{-1}; HRMS (EI): Calcd for $C_{31}H_{35}NO_3(M)^+$ 469.2617, found 469.2640.

General procedure for the tandem *N*-alkylation/bromination/1,4-addition (Scheme 7). Under an argon atmosphere, a suspension of β,γ-Alkenyl α-iminoester **4** (0.10 mmol) in THF (2.0 mL) was stirred at -78 °C for 5 min, and to it was added EtMgBr in THF solution (1.1 equiv). After stirring for 5 min at -78 °C, the mixture was warmed to 40 °C immediately and stirred for 20 min. After the consumption of substrate was confirmed by TLC, the mixture was cooled to 0 °C and stirred for 5 min, and to it was added NBS (1.5 equiv). After stirring for 15 min, to it was added copper reagent in THF solution (1.2 equiv), which was prepared by mixing CuCN (1.2 equiv) in THF (2.0 mL) and EtMgBr in THF (1.2 equiv) at 0 °C for 40 min, and the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. $NaHCO_3$ aq. (3.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 10 / 1) to give the desired compound.

Ethyl (*Z*)-2-[ethyl(4-methoxyphenyl)amino]-4,4-diphenylhex-2-enoate (10). Yield 23%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (t, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 2.36 (q, *J* = 7.3 Hz, 2H), 2.94 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 4.09 (q, *J* = 7.1 Hz, 2H), 6.32-6.36 (m, 2H), 6.66-6.70 (m, 2H), 7.13-7.25 (m, 10H), 7.54 (s, 1H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 9.9, 12.0, 14.1, 30.6, 45.8, 53.2, 55.6, 60.9, 114.1, 114 6, 126.0, 127.8, 128.4, 134.8, 141.2, 144.8, 145.8, 151.7, 167.6; IR(neat) 2933, 1717, 1684, 1653, 1559, 1541, 1509, 1457, 1376, 1242, 1036, 819, 755, 701, 562 cm^{-1}; HRMS(EI): Calcd for $C_{29}H_{33}NO_3(M)^+$ 443.2460, found 443.2476.

Ethyl (2Z)-2-[ethyl(4-methoxyphenyl)amino]-4-phenylhexa-2,4-dienoate (11). Yield 18%; Yellow oil; (*dr* = 75 : 25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 2.25H), 1.12 (t, *J* = 7.6 Hz, 0.75H), 1.66 (d, *J* = 7.3 Hz, 0.75H), 1.85 (d, *J* = 7.3 Hz, 2.25H), 2.94 (q, *J* = 7.2 Hz, 0.5H), 3.09 (q, *J* = 7.0 Hz, 1.5H), 3.73 (s, 2.25H), 3.74 (s, 0.75H), 4.10 (q, *J* = 7.0 Hz, 0.5H), 4.11 (q, *J* = 7.0 Hz, 1.5H), 5.93 (q, *J* = 7.2 Hz, 0.75H), 6.25-6.33 (m, 0.75H), 6.38-6.42 (m, 1.5H), 6.67-6.70 (m, 2H), 6.94-7.00 (m, 1.25H, including singlet at 7.00 ppm, 0.75H), 7.09-7.19 (m, 4.75H, including singlet at 7.19 ppm, 0.25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 14.0, 14.1, 15.5, 15.7, 45.1, 45.6, 55.6, 55.7, 60.8, 61.0, 114.1, 114.1, 114.2, 114.3, 114.9, 115.0, 115.8, 115.9, 126.0, 126.8, 126.9, 127.3, 127.6, 127.9, 128.6, 130.7, 135.2, 137.0, 137.2, 137.8, 140.2, 141.0, 151.6, 152.3, 167.8, 167.8; IR(neat) 2974, 2931, 1719, 1510, 1460, 1390, 1241, 1183, 1127, 1037, 821, 701 cm^{-1}; HRMS(EI): Calcd for $C_{23}H_{27}NO_3(M)^+$ 365.1991, found 365.1991.

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Supporting Information

NMR spectra. This material is available on http://dx.doi.org/10.1246/bcsj.***.

References

1. For *C*-alkylation to α-imino esters: a) J. -C. Fiaud, H. B. Kagan, *Tetrahedron Lett.* **1970**, *11*, 1813. b) L. M. Harwood, K. J. Vines, M. G. Drew, *Synlett* **1996**, 1051. c) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548. d) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, III., *J. Am. Chem. Soc.* **2002**, *124*, 1842. e) M. Mitani, Y. Tanaka, A. Sawada, A. Misu, Y. Matsumoto, *Eur. J. Org. Chem.* **2008**, 1383. f) P. Fu, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 5530. g) S. Fustero, N. Mateu, L. Albert, J. L. Aceña, *J. Org. Chem.* **2009**, *74*, 4429.
2. For *N*-alkylation to α-imino esters: a) J. -C. Fiaud, H. B. Kagan, *Tetrahedron Lett.* **1971**, *12*, 1019. b) Y. Yamamoto, W. Ito, *Tetrahedron* **1988**, *44*, 5415. c) K. Uneyama, F. Yan, S. Hirama, T. Katagiri, *Tetrahedron Lett.* **1996**, *37*, 2045. d) S. E. Yoo, Y. D. Gong, *Heterocycles* **1997**, *45*, 1251. e) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *Synlett* **1999**, 1148. f) M. Mae, H. Amii, K. Uneyama, *Tetrahedron Lett.* **2000**, *41*, 7893. g) K. P. Chiev, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2002**, *13*, 2205. h) J. S. Dickstein, M. W. Fennie, A. L. Norman, B. J. Paulose, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 15794. i) J. S. Dickstein, M. C. Kozlowski, *Chem. Soc. Rev.* **2008**, *37*, 1166. j) J. M. Curto, J. S. Dickstein, S. Berritt, M. C. Kozlowski, *Org. Lett.* **2014**, *16*, 1948.
3. For *N*-alkylation to α-imino esters in our laboratory: a) M. Shimizu and Y. Niwa, *Tetrahedron Lett.* **2001**, *42*, 2829. b) Y. Niwa, K. Takayama and M. Shimizu, *Tetrahedron Lett.* **2001**, *42*, 5473. c) Y. Niwa, K. Takayama and M. Shimizu, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1819. d) Y. Niwa and M. Shimizu, *J. Am. Chem. Soc.* **2003**, *125*, 3720. e) M. Shimizu, H. Itou and M. Miura *J. Am. Chem. Soc.* **2005**, *127*, 3296. f) M. Shimizu, *Pure Appl. Chem.* **2006**, *78*, 1867. g) M. Shimizu, I. Hachiya and I. Mizota, *Chem. Commun.* **2009**, 874. h) I. Mizota, K. Tanaka and M. Shimizu, *Tetrahedron Lett.* **2012**, *53*, 1847. i) T. Nishi,

I. Mizota and M. Shimizu, *Pure Appl. Chem.* **2012**, *84*, 2609. j) S. Hata, T. Maeda and M. Shimizu, *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1203. k) M. Shimizu, Y. Takao, H. Katsurayama and I. Mizota, *Asian J. Org. Chem.* **2013**, *2*, 130. l) M. Shimizu, D. Kurita and I. Mizota, *Asian J. Org. Chem.* **2013**, *2*, 208. m) T. Sano, I. Mizota and M. Shimizu, *Chem. Lett.* **2013**, *42*, 995. n) I. Mizota, Y. Matsuda, S. Kamimura, H. Tanaka and M. Shimizu, *Org. Lett.* **2013**, *15*, 4206. o) H. Tanaka, I. Mizota and M. Shimizu, *Org. Lett.* **2014**, *16*, 2276. p) M. Shimizu, M. Tateishi and I. Mizota, *Chem. Lett.* **2014**, *43*, 1752. q) I. Mizota, T. Maeda and M. Shimizu, *Tetrahedron* **2015**, *71*, 5793. r) I. Mizota and M. Shimizu, *Chem. Rec.* **2016**, *16*, 688.

4. For tandem 1,4-addition/aldol reaction: a) K. K. Heng, R. A. J. Smith, *Tetrahedron* **1979**, *35*, 425. b) K. Yoshida, M. Ogasawara, T. Hayashi, *J. Am. Chem. Soc.* **2002**, *124*, 10984. c) K. Subburaj, J. Montgomery, *J. Am. Chem. Soc.* **2003**, *125,* 11210. d) K. C. Nicolaou, W. Tang, P. Dagneau, R. Faraoni, *Angew. Chem. Int. Ed.* **2005**, *44*, 3874. e) M. K. Brown, S. J. Degrado, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2005**, *44*, 5306. f) G. P. Howell, S. P. Fletcher, K. Geurts, B. ter Horst, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 14977.
5. For reviews of vinylogous aldol-type reaction: a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076. b) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929.
6. For directive vinylogous aldol-type reaction: a) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813. b) S. Saito, M. Shiozawa, H. Yamamoto, *Angew. Chem. Int. Ed.* **1999**, *38*, 1769. c) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 14440. d) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 7439. e) J. C. Aponte, G. B. Hammond, B. Xu, *J. Org. Chem.* **2009**, *74*, 4623. f) J. Zhang, L. Gu, Y. Gong, *Synlett* **2012**, *23*, 468. g) J. A. Gazaille, T. Sammakia, *Org. Lett.* **2012**, *14*, 2678.
7. a) L. F. van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195. b) D. J. Peterson, *J. Org. Chem.* **1968**, *33*, 780.
8. C. Praveen, A. Ayyanar, P. T. Perumal, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4170.
9. a) J. P. Schneider, J. W. Kelly, *Chem. Rev.* **1995,** *95*, 2169. b) G. Tuchscherer, M. Mutter, *Pure Appl. Chem.* **1996**, *68*, 2153.
10. a) C. Danzin, P. Casara, N. Claverie and B. W. Metcalf, *J. Med. Chem.* **1981**, *24*, 16-20; b) M. L. Pedersen and D. B. Berkowitz, *J. Org. Chem.* **1993**, *58*, 6966.
11. a) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986. b) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem. Int. Ed.* **2007**, *46*, 4504. c) A. Calone, G. Bartoli, M. Bosco, F. Pesciaioli, R. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492. d) X. Lu, L. Deng, *Angew. Chem. Int. Ed.* **2008**, *47,* 7710. e) B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2009**, *48*, 4349. f) Q. X. Guo, Y. G. Peng, J. W. Zhang, L. Song, Z. Feng, L. Z. Gong, *Org. Lett.* **2009**, *11*, 4620. g) X. Tian, Y. Liu, P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 6439. h) X. Tian, P. Melchiorre, *Angew. Chem. Int. Ed.* **2013**, *52*, 5360. i) L. D. Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063. j) M. H. Zhou, Y. J. Jiang, Y. S. Fan, Y. Gao, S. Liu, S. Zhang, *Org. Lett.* **2014**, *16*, 1096.
12. L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

Graphical Abstract

<Title>

Synthesis of δ-Lactone and Amino Acid Frameworks Utilizing the Umpoled Reactivity of β,γ-Alkenyl α-Iminoester

<Authors' names>

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<Summary>

An umpolung *N*-alkylation reaction of β,γ-alkenyl α-iminoesters was studied, and various tandem reactions were found utilizing this *N*-alkylation. A novel synthesis of δ-lactones and α-quaternary alkenyl amino esters was developed by tandem *N*-alkylation/vinylogous aldol-type reaction and the tandem *N*-alkylation/bromination/*C*-alkylation, which these methods are operationally simple and useful, and exhibit broad substrate generality.

<Diagram>