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Diastereoselective Conjugate 1,6-Addition of Lithium Amides to Naphthyloxazolines. Mechanistic Studies and Synthesis of δ-Amino Acid Derivatives.

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Abstract

The novel 1,6-amino addition reaction to the naphthalene ring system followed by the electrophilic alkylation is presented. The detailed mechanistic studies suggest the existence of two equilibrations that result in the 1,4-amino addition reaction and the 1,6-amino addition reaction. The stability and bulkiness of lithium amide play a key role in directing the course of the reaction. The transformation of the 1,6-amino adducts to other useful compounds is concisely demonstrated. The methodology provides a remote-controlled diastereoselective synthesis of δ-amino acid derivatives.

Keywords: Regiocontrol; Diastereoselection; Stereocontrol; Oxazolines/oxazolinones.

Introduction

Several reactions involving 1,6-*substitution* of an amino function on an aromatic ring system have been reported as a very useful tool for the syntheses of 4-substituted aniline derivatives.[1-4] On the other hand, the reaction involving 1,6-*addition* of an amino function to an aromatic ring system, which thus interrupts the aromaticity and leads to the alicyclic amine, has remained to be an object of study because of the lack of examples and its potential utilities. Recently, we reported, in a preliminary manner, a direct amination of the naphthyloxazoline in the style of 1,6-amino addition followed by electrophilic quenching to provide δ-amino, α-alkyl, α-oxazolinylnaphthalenes.[5] We now wish to describe this novel, regioselective direct amination reaction in detail which involves the exploration of the optimal reaction conditions, more examples with a variety of lithium amides, mechanistic observations and a synthesis of a new class of δ-amino acid derivatives, and also to present the transformation of the 1,6-amino adduct to other synthetically useful compounds.

Results and discussion

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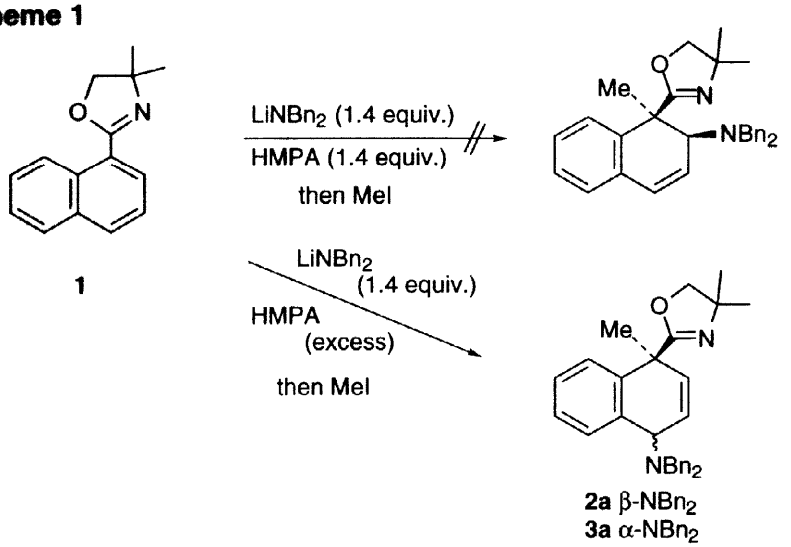
1,6-Amino addition reaction of lithium amides to naphthyloxazolines

During the effort to define the effectiveness and scope of the 1,4-amino addition reaction,[6,7] another synthetically remarkable reaction was serendipitiously observed. When lithium dibenzylamide, a relatively bulky lithium amide was subjected to the typical 1,4-addition reaction conditions (1.4 equivalents of lithium amide and 1.4 equivalents of HMPA were used with naphthyloxazoline **1**),[6,7] the 1,4-addition reaction was not observed and the starting naphthyloxazoline **1** was completely recovered. However, we found a novel fact that lithium dibenzylamide with excess HMPA attacked the δ position of naphthyloxazoline **1** affording 1,6-amino adducts **2a** and **3a** (Scheme 1).[1] Any trace of the normal 1,4-amino adduct was not detected in this case. The uniqueness and the potential usefulness of this 1,6-amino addition reaction prompted us to further investigations, though we did not understand the reason why the reaction with lithium dibenzylamide gave 1,6-amino adducts selectively.

Scheme 1



First of all, the reaction was scrutinized in THF by varying the amount of HMPA in order to reach the optimized conditions (Table 1). In every entry, we could not detect any trace of 1,4-amino adduct products, so that the addition of lithium dibenzylamide occurred regiospecifically at the δ position, though the plausible reason remained to be seen. The electrophilic quench of the consequent azaenolate anion (in these cases, MeI) occurred at the α position to the oxazoline group in preference to the γ position (about 10 : 1) and its stereoselectivity was about 5 : 1. From the results (from entry 1 to entry 5), the existence of a large excess HMPA was crucial to the successful addition of lithium dibenzylamide. After all, we have reached the conclusion that the ratio of HMPA-THF (1 : 4) was best for the completion of these 1,6-amino addition reactions.[2] Because a large amount of DMPU (entry 6) did not afford any good results at all, HMPA should have two important roles as a coordinating reagent and as a co-solvent to change the character of the reaction medium.

Now that the optimal reaction conditions are known, we undertook experiments to examine a variety of lithium amides in the presence of sufficient HMPA.

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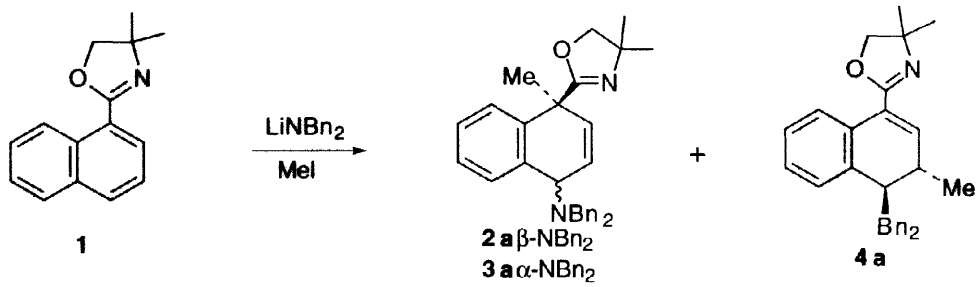
1. All new materials were fully characterized. See the experimental section.
2. The addition of lithium diallylamide and lithium *N*-methyl-*N*-benzylamide can be conducted with slightly less HMPA.

Table 1. Effect of HMPA (equiv.) and DMPU in the Regioselective Addition of Lithium Dibenzylamide to 1-Naphthyloxazoline **1**.



1 **2a**β-NBn_2 **3a**α-NBn_2 **4a**

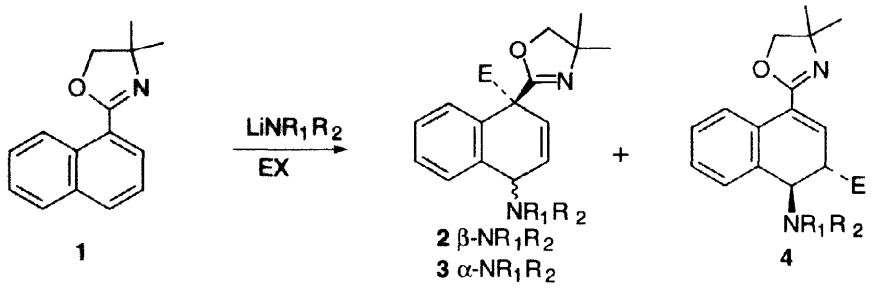
entry[a]	$LiNBn_2$ (equiv.)	HMPA (equiv.)	MeI (equiv.)	ratio[b] product(**2a**+**3a**+**4a**)[c]	S.M. recovery
1	2.0	2.0	2.5	0	100
2	1.6	3.2	1.9	1.5	98.5
3	1.6	4.8	1.9	14.7	85.3
4	1.6	9.6	1.9	87.2[d]	12.8
5	1.6	16.0	1.9	>99[d]	<1
6	1.6	DMPU[e]	1.9	3.3	96.7

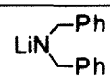
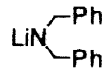
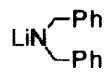
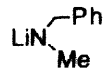
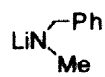
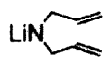
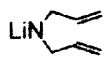
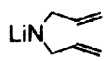
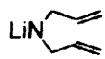
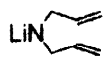
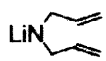
a. Unless otherwise noted, all reactions were carried out at -78 °C and allowed to warm to between -65 °C and -60 °C under the same conditions. b. Ratio determined by ^{1}H-NMR (270MHz, $CDCl_3$) crude mixture. c. In each case, other kinds of products were not observed and a quantitative mass balance was obtained. d. About 10% of 1,6-addition-1,5-quenched product **4a** was observed. e. 16.0 equiv. of DMPU was used.

The results were that the lithium amides affording 1,4-amino adducts in the presence of stoichiometric HMPA[6,7] still gave 1,4-adducts very predominantly under the conditions for the 1,6-amino addition reaction,[3] but that the particular lithium amides shown in Table 2 (entries 1~12)[4] afforded 1,6-amino adducts exclusively. The stereo- and regiochemistry of all products were determined by the chemical shifts and coupling constants of ^{1}H-NMR spectra along with the NOE experiments for some products. Furthermore, two of the major products, **2c** and **2g**, were determined unequivocally by performing single crystal X-ray analyses.[5] The stereochemistry of an electrophilic quenching at the last stage of this reaction seemed to be dominated mainly by the bulkiness of the electrophile. For example, a bulky benzyl bromide and allyl bromide were exclusively trapped from the opposite to the newly installed amino group and gave 1,6-*trans*-products **2** (entries 2-5, 10 and 12), while a smaller methyl iodide afforded 1,6-*trans*-product **2** as a major product on the same stereoselective course with the case of benzyl bromide, but concomitant with a small amount of 1,6-*cis*-adducts **3** (entries 1 and 6). On the other hand, the regiochemical course had been a little confusing. The bulky benzyl bromide was exclusively trapped at the carbon attached to the oxazoline group to give the normal 1,3-quenched products **2** (entry 3, 5 and 12), while the smaller methyl iodide and allyl bromide had a bypath to give the 1,5-quenched products **4**.

3. The ratio of the 1,4-adducts and 1,6-adducts in the case of lithium piperidide was 98 : 2.
4. These lithium amides gave no 1,4- amino adducts in the presence of stoichiometric HMPA.
5. The author has deposited atomic coordinates for **2c** and **2g** with Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 2. Regiospecific 1,6-Addition of Lithium Amides to **1**.

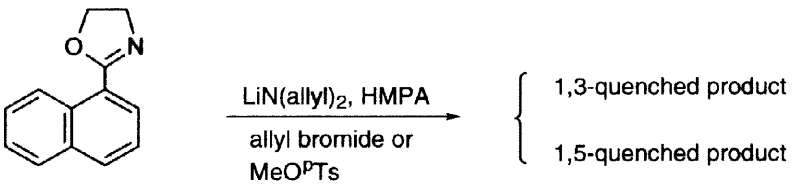


entry	R_1R_2NLi [a]	electrophile (EX)	product ratio[b] (**2** : **3** : **4**)	products(%)[c]
1		MeI	78 : 15 : 7	**2a**+**3a**(88),[d] **4a**(5)
2			91 : <1 : 9	**2b**(84), **4b**(5)
3		BnBr	>98 : <1 : <1	**2c**(93)
4			89 : <2 : 9	**2d**(86), **4d**(6)
5		BnBr	>98 : <1 : <1	**2e**(94)
6		MeI	75 : 15 : 10	**2f**+**3f**(88),[e] **4f**(7)
7		MeO^pTs	83 : 17 : <1	**2f**+**3f**(60) [f]
8		MeOBs	83 : 17 : <1	**2f**+**3f**(55) [g]
9		MeOTf	83 : 17 : <1	**2f**+**3f**(92)
10			91 : <1 : 9	**2g**(87), **4g**(6)
11			46 : <1 : 54	**2h**(43), **4h**(49)
12		BnBr	>98 : <1 : <1	**2i**(92)

a. The lithium amides were prepared *in situ* from the corresponding amines and ^{n}BuLi. b. Ratios determined by ^{1}H-NMR (270MHz, $CDCl_3$) of crude mixture. c. Isolated yields. d. Careful silica gel column chromatography could separate **2a** and **3a** from each other, but the yield was lowered. e. Recrystallization could give nearly pure **2f**(>30 : 1). f. 25 % of **1** was recovered. g. 18 % of **1** was recovered.

Prenyl bromide, a bulkier molecule than allyl bromide, however, gave almost a 1 : 1 mixture of 1,3- and 1,5-quenched products **2h** and **4h** (entry 11). Because of no production of the 1,6-*cis* product, this result did not seem to come from the bulkiness of the electrophile, and we considered whether the course was dominated by the hard and soft acid-base theory.[8-10] A typical hard acid, methyl *p*-tosylate (entry 7), was examined instead of methyl iodide, and it gave the 1,3-quenched products **2f** and **3f**, but the 1,5-quenched product **4f** was not detected at all. The same results were observed with other

sulfonates (entries 8 and 9), and methyl triflate afforded a superior yield.[11] Because every methylating reagent gave exactly the same ratio between 1,6-*trans*-adduct **2f** and 1,6-*cis*-adduct **3f**, the bulkiness of the counterpart of the methylating reagent (*i.e.* iodide, *p*-tosylate etc.) had nothing to do with the stereochemical outcome. In order to further define the difference in the character between methyl iodide and prenyl bromide, the transition states of each 1,3- and 1,5-quenched product of both cases were calculated with semiempirical molecular orbital methodology (AM1 Hamiltonian) implemented in MOPAC version 6.0.[12,13][6,7] In the case of methyl iodide, ΔE between 1,3- and 1,5-quenched intermediates was 1.23kcal/mol. ΔE in the case of prenyl bromide was 3.93kcal/mol. In both cases, 1,5-quenched intermediates were calculated to be favored. Though the calculations were carried out under the simplified conditions and the calculation results did not match well with the real outcome,[8] it was shown qualitatively that prenyl bromide had a stronger tendency to give the 1,5-quenched product than methyl iodide.



5

Furthermore, we prepared another kind of naphthyloxazoline **5** which had a less hindered space around the oxazoline group and examined it with lithium diallylamide followed by allyl bromide or methyl *p*-tosylate. In both cases, the ratio between 1,3-quenched- and 1,5-quenched-product was very similar to the case of **1**, though the reactions were not as clean as those of **1**. Based upon these results, the electrophilic quenching site was very likely to be induced by the character of the carbon according to the HSAB theory.[9]

Mechanistic Studies

We have tried to determine what induced the 1,6-amino addition reaction instead of the 1,4-amino addition reaction ever since the first 1,6-amino addition was observed. As mentioned before, the lithium amides with stoichiometric HMPA giving 1,4-amino adducts still afforded 1,4-adducts very predominantly in the presence of a large amount of HMPA, so that HMPA just accelerated the amino addition reaction and did not seem to play a pivotal role in determining the addition route. This meant that the character of the lithium amide itself had a crucial role in inducing the 1,6-amino addition reaction. A characteristic common to all of the lithium amides giving 1,6- amino adducts in Table 2 was that the amino nitrogen was attached to a double bond carbon through one sp^3 carbon and that all of

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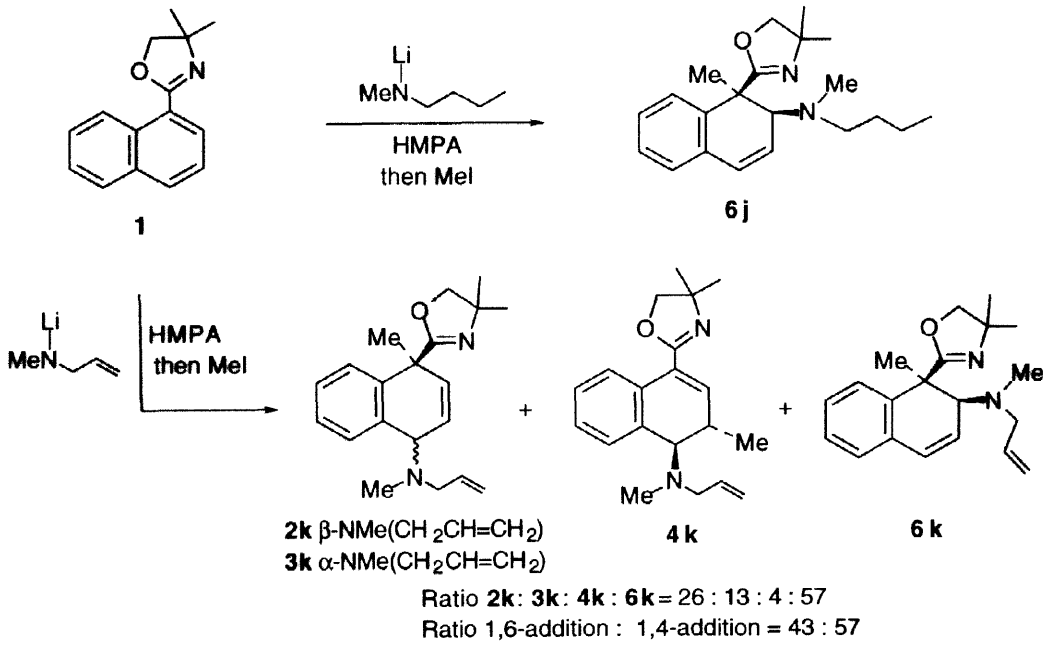
6. Though the effect of HMPA and Li^+ should not be ignored, we demonstrated the calculation with the omission of HMPA and Li^+ because of the uncertainty about how many HMPA molecules were involved and where Li^+ was situated in the transition state .
7. In order to simplify the calculations, the diallylamino group was replaced with a dimethylamino group.
8. The omission of Li^+ has appeared to influence the results greatly. The replacement of the diallylamino group with a smaller dimethylamino group may also cause the 1,5-quenched intermediates to be favored in both cases.
9. Prenyl bromide seemed to be a considerably soft electrophile according to the fact that potassium phenoxide was completely C-alkylated with prenyl bromide ; See (a) Mori, K.; Takanashi,.S. *Proc. Japan Acad.* **1996**, 72(B), 174. (b) Bu, X.; Li, Y. *J. Nat. Prod.* **1996**, *59*, 968.

the lithium amides prepared had a respective color. With those hints in mind, we started to analyze chemically what happened in the flask.

First of all, we selected lithium *N*-methyl-*N*-allylamide which had the same feature as the lithium amides in Table 2 as mentioned above and, at the same time, whose bulkiness was as small as that of lithium *N*-methyl-*N*-butylamide that has been known to give 1,4-amino adduct **6j**. Under the typical conditions for the 1,6-amino addition reaction, the reaction of **1** with lithium *N*-methyl-*N*-allylamide followed by MeI quenching gave a mixture of four products as shown in Scheme 2. The ratio of 1,6-addition products (**2k**, **3k** and **4k**) to 1,4-addition product **6k** was 43 to 57.

Scheme 2



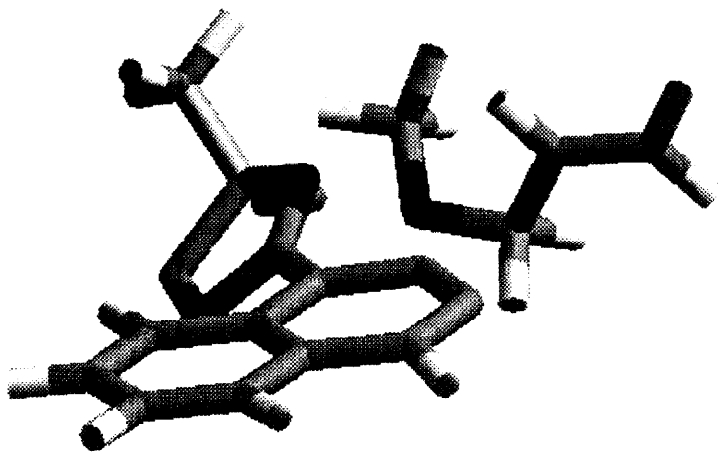
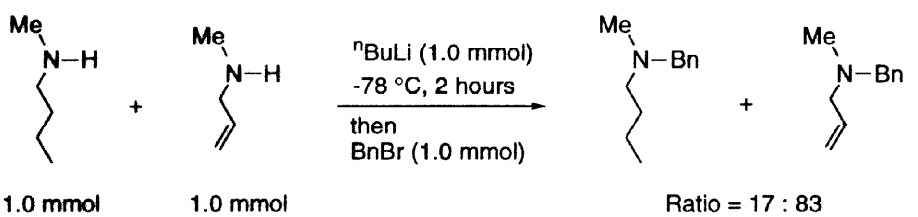


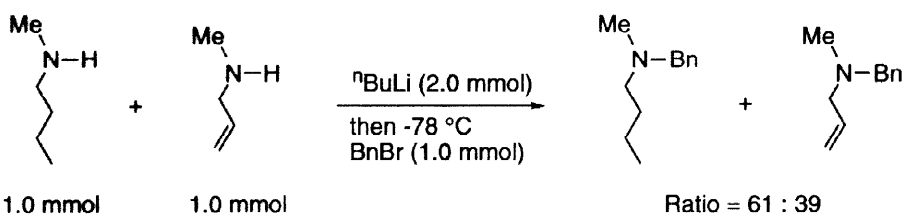
Figure 1. The Transition State of 1,6-Amino Addition of Lithium *N*-Methyl-*N*-Allylamide to Naphthyloxazoline **1**. Some of the Hydrogens are Omitted for Clarity.

Because the difference in bulkiness between lithium *N*-methyl-*N*-butylamide and lithium *N*-methyl-*N*-allylamide seemed to be small, there should be a great difference in electronic features between them. Therefore, the transition state of 1,6-amino addition of lithium *N*-methyl-*N*-allylamide to naphthyloxazoline **1** was calculated with MOPAC version 6.0.[12,13] We had initially thought that the π–π stacking between the naphthalene ring and the allyl group on nitrogen should exist and that this should be the primary driving force to allow the 1,6-amino addition reaction to prceed. However, as shown in Figure 1, the allyl group attached to nitrogen occupied a position far away from the naphthalene ring to minimize the steric hindrance and no π–π stacking appeared between them.[10] Because there should be something to promote the 1,6-amino addition reaction, we then examined the relative acidities between the parent amines (Scheme 3). A stoichiometric mixture of *N*-methyl-*N*-butylamine (1.0 mmol) and *N*-methyl-*N*-allylamine (1.0 mmol) in THF at -78 °C was treated with *n*-butyllithium (1.0 mmol) for 2 hours and then quenched with benzyl bromide (1.0 mmol) at -78 °C. The product ratio between *N*-methyl-*N*-butyl-*N*-benzylamine and *N*-methyl-*N*-allyl-*N*-benzylamine was 17 : 83,[11] so that *N*-methyl-*N*-allylamine was easier to deprotonate than *N*-methyl-*N*-butylamine.

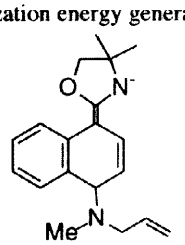
Scheme 3



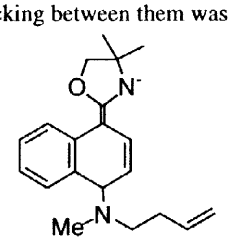
Scheme 4



10. This result does not completely rule out the route associated with the π–π stacking between the aromatic ring and the allyl group, because it is rather difficult to calculate the transition state properly when there is another interaction between a substrate and a reagent at other places besides the reaction point that makes the energy diagram change ragged. However, we have also calculated the most stable conformations of the intermediate **A** and the imaginary intermediate **B** if intramolecular π–π stacking might occur. It turned out in both cases that there seemed to be no π–π stacking between the aromatic ring and the allyl group and that the allyl group occupied the space to avoid any interaction from other functional groups. Thus the stabilization energy generated by the π–π stacking between them was not as large as we had imagined.



A

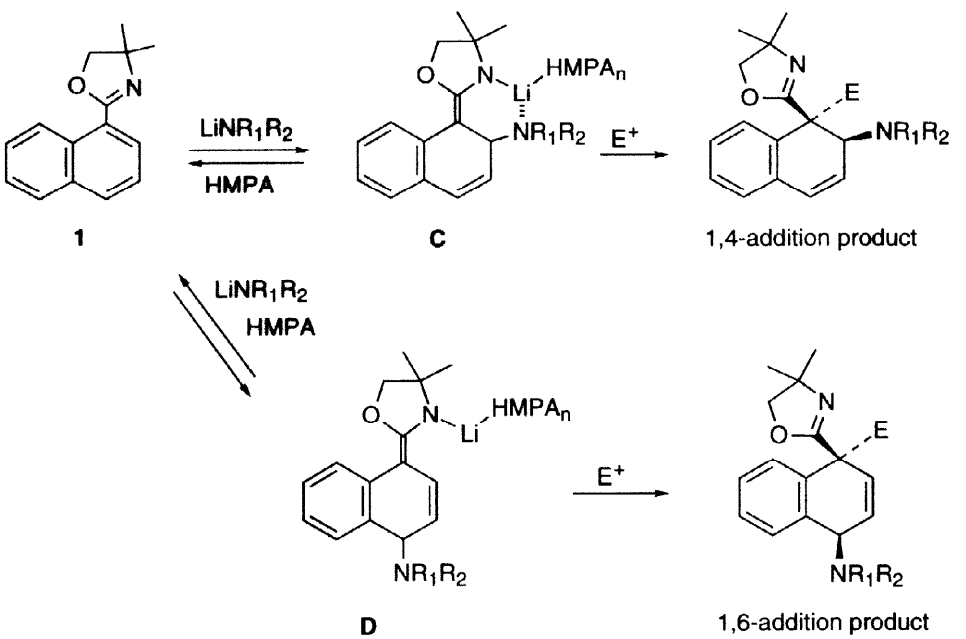


B

11. Quantitative mass balance was obtained.

It was likely that the allyl group made the amine proton more acidic than the saturated alkyl group did and that the corresponding lithium amide was more stable than the ordinary lithium amide. This meant that the p*Kb* of lithium *N*-methyl-*N*-allylamide was smaller than that of lithium *N*-methyl-*N*-butylamide. The relative nucleophilicity between lithium *N*-methyl-*N*-butylamide and lithium *N*-methyl-*N*-allylamide was also examined (Scheme 4), and appeared to be little difference in the nucleophilicity between them.These results and the previous observation, which has shown the existence of an equilibrium between the starting naphthyloxazoline with lithium amide and the azaenolate intermediate in the case of 1,4-amino addition reaction,[7] suggested that another equilibration would exist between the 1,4-amino adduct intermediate **C** and the 1,6-amino adduct intermediate **D** through the starting naphthyloxazoline **1** as depicted in Scheme 5.[12] Based on this assumption, we examined the product ratio under various conditions by changing the temperature and the reaction time. First, the reaction between naphthyloxazoline **1** and lithium *N*-methyl-*N*-allylamide was performed at below -65 °C for 3 hours, and iodomethane quenching gave 1,4-amino adduct **6k** as the sole product, though a considerable amount of starting material was recovered.[13,14] Prolongation of the reaction time (8 hours) did not change the product proportion so that the 1,6-amino addition reaction never occurred at below -65 °C. However, when the reaction was conducted at below -65 °C for 5 hours, then warmed to -50 °C and kept at -50 °C for 3 hours, iodomethane quenching gave 1,4-amino adduct **6k** along with 1,6-addition products (**2k**, **3k** and **4k**) in the ratio 83 : 17.

Scheme 5



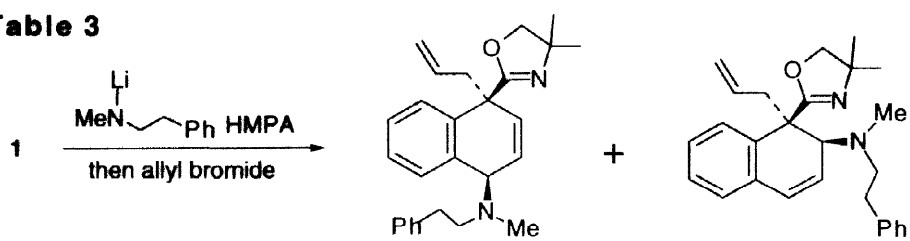
12. Because the addition of an electrophile into the reaction mixture is always conducted at -78°C and the trapping of azaenolate anions with the electrophile is usually completed below -50°C, the reaction rate of the azaenolate anions with the electrophile does not seem to reflect the regioselectivity directly.
13. A stoichiometric amount of HMPA with lithium *N*-methyl-*N*-allylamide was used because a large excess of HMPA precipitated at low temperature.
14. We also checked the reaction of lithium *N*-methyl-*N*-allylamide with H_2O as an electrophile in order to obtain protonated amino adducts, but the results were that only starting oxazoline **1** was completely recovered. The azaenolate anion intermediates were definitely generated in situ; therefore, the driving force to return to the naphthalene aromaticity drew back the reaction with the help of H_2O and restored the starting oxazoline **1** and *N*-methyl-*N*-allylamine.

These results have clearly revealed that there was an equilibrium between them and that, at the same time, the 1,4-amino adduct was a kinetically controlled product but the 1,6-amino adducts were thermodynamically produced at higher temperature (~-50 °C). The stability of lithium amide appeared to reflect the reversibility of both the 1,4-amino adduct intermediate **C** to **1** and the 1,6-adduct intermediate **D** to **1** equally (Scheme 5). However, because the 1,6-adduct intermediate **D** was thermodynamically more stable than the 1,4-amino adduct intermediate **C**, the equilibration point shifted from the 1,4-adduct intermediate **C** to the 1,6-adduct intermediate **D** at higher temperature.

We then selected 3-pyrroline, a cyclic allyl amine, whose bulkiness was as small as that of pyrrolidine. In contrast to pyrrolidine, which has been known to give the 1,4-amino adduct in excellent yield, the reaction of lithium 3-pyrrolide with naphthyloxazoline **1** in the presence of HMPA always gave a complicated inseparable mixture.[15] Many unidentified by-products made the crude ^{1}H-NMR spectrum difficult to analyze; therefore, it was difficult to identify the characteristic signals for the 1,4-amino adduct product, but the characteristic signals for the 1,6-amino adduct products seemed to be observed. Because the steric bulkiness between pyrrolidine and 3-pyrroline was almost the same, the results in the 3-pyrroline case apparently reflected its electronic characteristics.

Our attention was then focused on lithium *N*-methyl-*N*-phenethylamide whose amino nitrogen was attached by a double bond through *two* sp^3 carbon to determine whether the 1,6-amino addition reaction would still dominate over the 1,4-amino addition reaction. Though the structure of lithium *N*-methyl-*N*-phenethylamide was similar to that of lithium *N*-methyl-*N*-benzylamide which afforded only the 1,6-amino adduct products (Table 2, entries 4 and 5), the results were rather interesting (Table 3).

Table 3



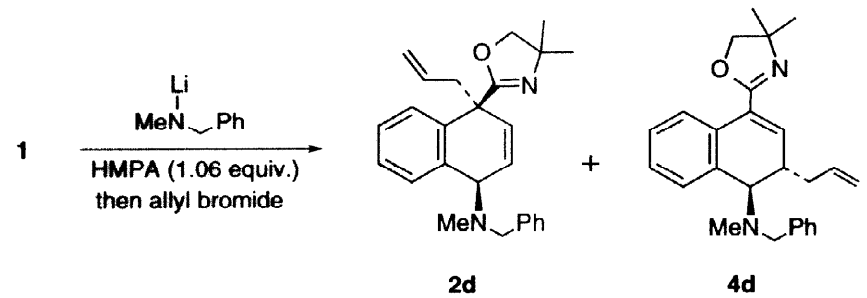
2l **6l**

entry[a]	HMPA (equiv.)[b]	temperature (°C)[c]	time (hours)[c]	product ratio (**2l**: **6l**)[d]	products(%)[e]
1	16	-60~-50	3	>99 : <1	**2l**(44)
2	2.1	-60~-50	3	>99 : <1	**2l**(31)[f]
3	1.06	-60~-50	3	22 : 78	**2l**(7), **6l**(32)[g]
4	1.06	-65	6	15 : 85	**2l**(5), **6l**(48)[h]

a. The lithium amide (1.6 equiv.) was prepared *in situ* from *N*-methyl-*N*- phenethylamine and ^{n}BuLi. b. Equivalents were measured against the lithium amide. c. The temperature and the time before adding allyl bromide. d. Ratios determined by ^{1}H-NMR (270MHz, $CDCl_3$) of crude mixture. e. Isolated yields. f. 42 % of **1** was recovered. g. 45 % of **1** was recovered. h. 33 % of **1** was recovered.

15. 3-Pyrroline (97 % purity) was purchased from Aldrich and used without further purification. The amount of HMPA and the reaction temperature were varied to achieve a better result, but these efforts were fruitless. Unfortunately, the desired products were unstable.

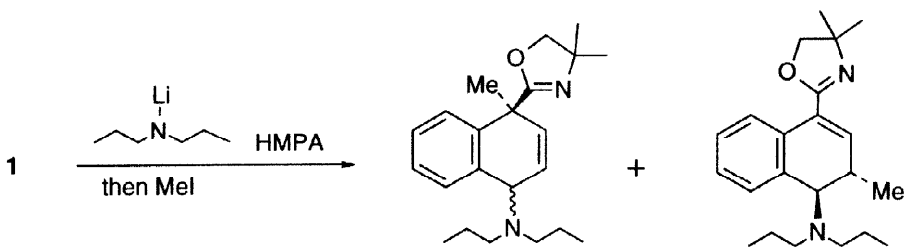
The typical conditions with a large amount of HMPA gave 1,6-amino adduct **2l** as a major product; however, several unidentified by-products were concomitantly formed (entry 1). The conditions using 2.1 equivalents of HMPA with lithium *N*-methyl-*N*-phenethylamide also afforded 1,6-amino adduct **2l** as a major product, though a large amount of starting oxazoline **1** was recovered (entry 2). In both cases, 1,4-adduct **6l** was not detected at all. On the other hand, under the conditions using 1.06 equivalents of HMPA with lithium *N*-methyl-*N*-phenethylamide, 1,4-adduct **6l** became a major product (entries 3 and 4). These results suggested that excess HMPA would participate in the domination of the 1,6-amino addition reaction in this case, although the course of lithium piperidide and lithium dibenzylamide were not influenced by the amount of HMPA. At this point, we reinvestigated lithium *N*-methyl-*N*-benzylamide which only afforded 1,6-amino adduct products in the presence of excess HMPA (Table 2, entries 4 and 5) because of the structural similarity to lithium *N*-methyl-*N*-phenethylamide.



2d **4d**

The result was that the combination of lithium *N*-methyl-*N*-benzylamide and 1.06 equivalents of HMPA still gave 1,6-amino adducts **2d** and **4d** as the only detectable products, although a large amount of starting material remained intact. In other words, the amount of HMPA did not affect the regiochemical course of amino addition reaction to lithium *N*-methyl-*N*-benzylamide. Thus lithium *N*-methyl-*N*-phenethylamide seemed to take a middle position where it could attack both positions to afford 1,4- and 1,6-amino adducts, and this seemed to be a quite rare case.

Because the electronic effect of lithium amide has been discussed in detail, the bulkiness of lithium amide was then examined to see if it was also important. Lithium di-*n*-propylamide was studied because of its structural similarity to lithium diallylamide which only gave 1,6-amino adduct products (Table 2, entries 6-12).



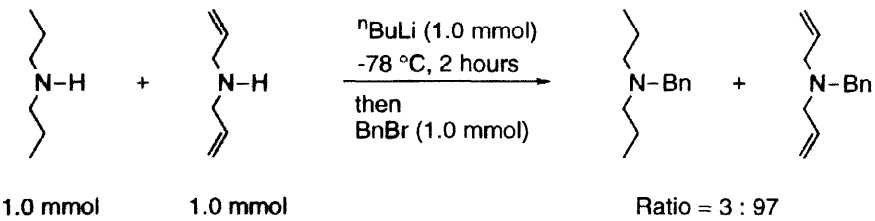
2m β-NPr_2
3m α-NPr_2

4m

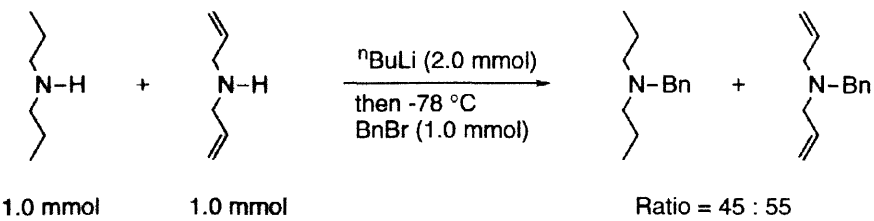
Ratio **2m** : **3m** : **4m** = 74 : 22 : 4
Ratio 1,6-addition : 1,4-addition = >99 : <1

Under the typical conditions for 1,6-amino addition reaction, lithium di-*n*-propylamide afforded 1,6-amino adducts **2m**, **3m** and **4m** as major products along with a small amount of starting material (~10 %) being always recovered. The corresponding 1,4-amino adduct was not detected; therefore the electronic character (acidities and nucleophilicities) of di-*n*-propylamine relative to that of diallylamine was measured (Schemes 6 and 7). The di-*n*-propylamine was found to be much less acidic than diallylamine, which was in accord with the results between *N*-methyl-*N*-butylamine and *N*-methyl-*N*-allylamine. Though the observation strongly suggested that the bulkiness of lithium di-*n*-propylamide prevented the 1,4-amino addition reaction completely and that lithium di-*n*-propylamide never approached the β-carbon to the oxazoline group, the small amount of starting material recovery also suggested that the 1,4-amino adduct intermediate may have existed but that the bulkiness of the two *n*-propyl groups may have hindered the approach of the electrophile such that the equilibrium favored a return to the starting material. As a matter of fact, lithium diallylamide in Table 2 always consumed the starting material completely and afforded 1,6-amino adduct products in excellent yield.[16]

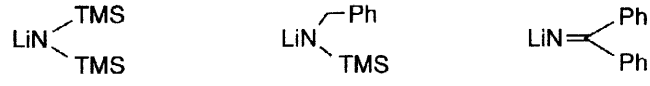
Scheme 6



Scheme 7



Three other kinds of bulky lithium amides (lithium bis(trimethylsilyl)amide, lithium benzyltrimethylsilylamide[14,15] and lithium benzophenone imine lithium salt) were also examined under the same conditions but the results were complete starting oxazoline recovery. The bulkiness of lithium amide was also one of the pivotal elements for the regioselective amino addition reaction, but the maximum permissible bulkiness of lithium amide did not seem to be very high, because three other bulkier lithium amides never attacked **1** to afford amino adduct product.

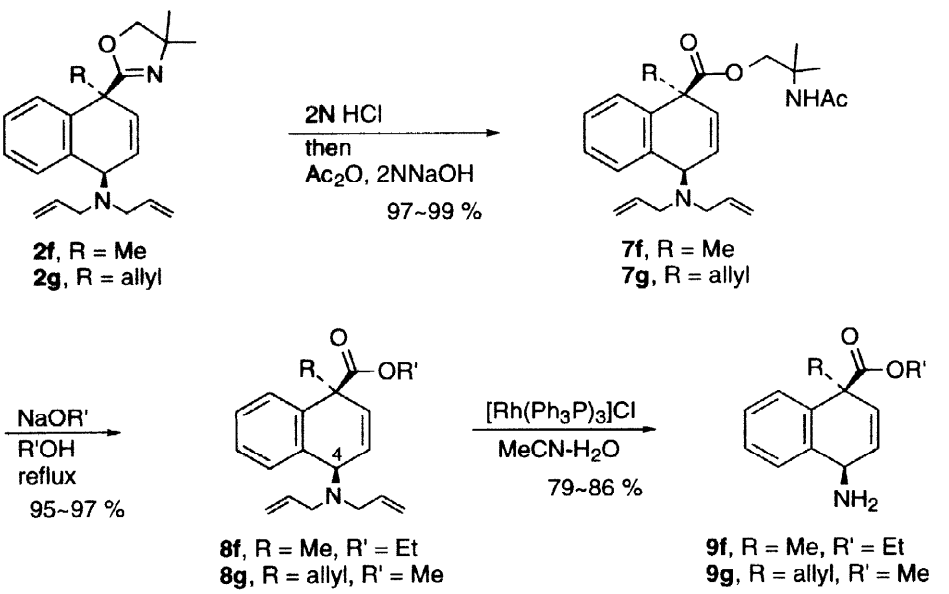


16. We have explained the reaction mechanism as an ionic reaction, but we do not rule out the possibility that the reaction proceeded from another kind of mechanism such as a one-electron reduction of naphthyloxazoline **1** with lithium amide.

δ-Amino acids synthesis.

Because of the usefulness and importance of the primary amino group, which can be converted to many kinds of secondary and tertiary amines as well as other types of amino functional groups, we demonstrated the synthesis of δ-amino acid esters **9f** and **9g** from the adducts, **2f** and **2g**, as shown in Scheme 8. The oxazoline groups were first removed in a two-step sequence by the procedure described previously,[7] providing esters **8f** and **8g** through amidoesters **7f** and **7g** respectively. After some disappointing results concerning the cleavage of the diallyl group to liberate a primary amino group using a Pd catalyst,[16] this reaction was successfully carried out using a Wilkinson catalyst to give δ-amino acid esters **9f** and **9g** respectively.[17] It should be stated that the C_4 position in **9** should be very reactive because of being both a benzylic and an allylic position, and yet the C-N bond of the diallylamino group was severed much faster than the C_4-N bond. Furthermore, in the case of **8g** which had an allyl side chain, we could not detect the double bond migration product (*i.e.*,1-allyl → 1-1'-propenyl). Using a simple four-step sequence, a flat naphthyloxazoline **1** could be converted to the three-dimensional δ-amino acid derivatives with high regio- and stereoselectivities and excellent chemical yields. The starting naphthyloxazoline **1** does not need any functional group at the δ position to the oxazoline group for amino function equipment and that makes this methodology very useful and practical.

Scheme 8



2f, R = Me
2g, R = allyl

7f, R = Me
7g, R = allyl

8f, R = Me, R' = Et
8g, R = allyl, R' = Me

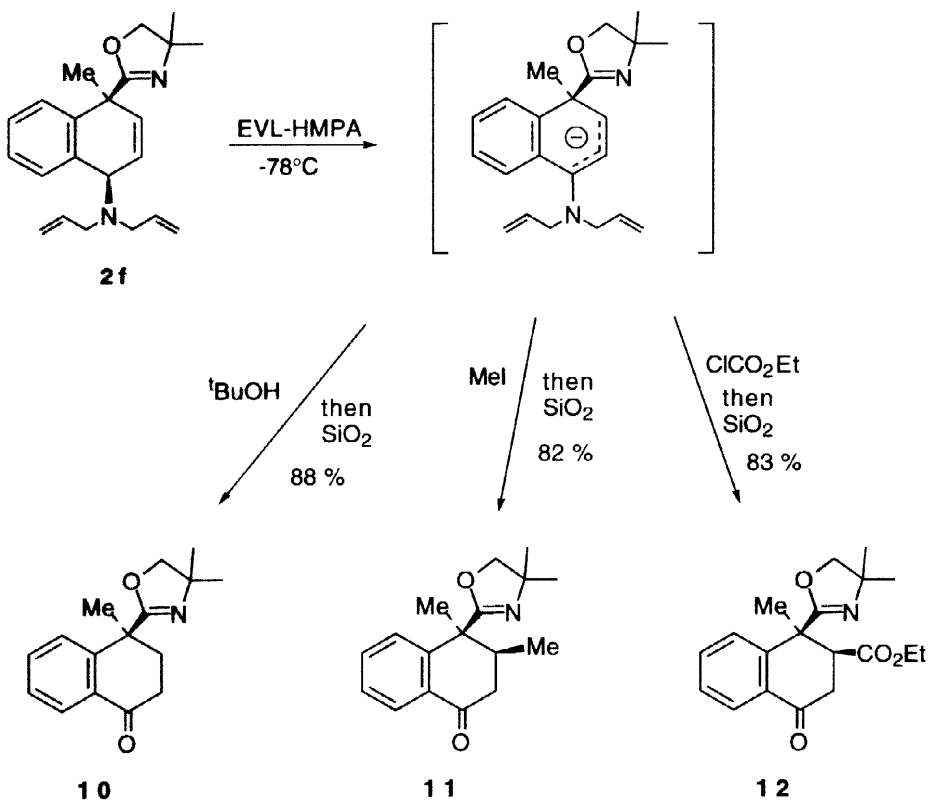
9f, R = Me, R' = Et
9g, R = allyl, R' = Me

Other chemical transformations

In order to further prove the usefulness of the 1,6-amino addition reaction, 1,6-amino adduct **2f** was transformed to another synthetically interesting compounds. As shown in Scheme 9, 1,6-amino adduct **2f** was treated with α-ethoxyvinyllithium-HMPA[18,19] to prepare the lithiated intermediate in bracket. An ordinary strong base such as *n*-

butyllithium,[20,21] *s*-butyllithium and *t*-butyllithium did not give a good result. The lithiated intermediate was then treated with an electrophile and a subsequent hydrolysis with silica gel afforded 2-substituted-4-oxa-1,2,3,4-tetrahydronaphthyloxazolines **10**, **11** and **12** respectively. Diastereoselectivity of methylation to give **11** was excellent (>95 : 5),[17] while the ethoxycarbonylation proceeded with 85 : 15 diastereoselectivity.[18] Perhaps this inferior selectivity appears to stem from the higher reactivity of ethyl chlorocarbonate or the quick isomerization of the newly installed asymmetric carbon attached to the ethoxycarbonyl group. It is worth mentioning that very long steps would be needed to prepare ethoxycarbonylated product **12** if the direct nucleophilic 1,4-alkylation reaction to naphthyloxazoline was employed because of the tedious transformation to the carbonyl function. Furthermore, if DMF was employed as an electrophile, an aldehyde function would be directly introduced.

Scheme 9



Conclusion

A novel, synthetically useful 1,6-addition reaction of several particular secondary amine lithium salts with 1-naphthyloxazoline **1** providing a remote-controlled stereoselective synthesis of δ-amino acid derivatives was revealed. The detailed mechanistic studies have suggested the existence of two equilibrations that result in 1,4-amino addition

17. There is no plausible explanation for the observed stereoselectivity so far.
18. The stereochemistry of the newly installed asymmetric carbon was determined by NOESY spectra in each case.

reaction and 1,6-amino addition reaction, respectively, and that the stability (basicity) and the bulkiness of lithium amide played a key role in deciding the course of the reaction. The transformation of the 1,6-amino adducts to other useful compounds was concisely demonstrated. Because there was no systematic research on 1,6-amino addition reaction until our preliminary report was published, we believe that this article will make an important contribution to the development of the 1,6-amino addition reaction. Further studies on the enantioselective sense of the 1,6-amino addition reaction are underway and will be reported in due course.

Experimental Section

Instrumentation

^1H and ^{13}C NMR spectra were recorded at 270 MHz and 67.8 MHz respectively on JEOL JNM-EX-270. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane, $CDCl_3$ with $CHCl_3$ as an internal reference (7.24 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR), or DMSO-d_6 with DMSO-d_5 as an internal reference (2.49 ppm for ^1H NMR and 39.5 ppm for ^{13}C NMR). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad). Infrared spectra were recorded on a Shimadzu FTIR-4200. Gas-chromatography-mass-spectrometry was performed with a Shimadzu GCMS-QP1000EX. Microanalyses were performed with a Yanaco CHN CORDER MT-5. Mass spectra were measured on a JEOL HX-110A. Melting points were obtained from a Yanaco MP-500D and are uncorrected. Thin layer chromatography was performed on E. Merck and Co. precoated silica gel $60F_{254}$ Column chromatography was carried out with E. Merck and Co. silica gel 60 (70-230 mesh ASTM).

Materials

Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use. HMPA and DMPU were purchased from Aldrich, dried over CaH_2 at 60 °C for 12 hours, distilled under reduced pressure (2 mmHg) and stored over 13X molecular sieves in a dark place. *n*-Butyllithium and *t*-butyllithium were purchased from Kanto Kagaku Co., Inc. Dichloromethane and all secondary amines were dried over 4A molecular sieves prior to use. All other reagents were purchased from Nakarai Tesque and used without further purification unless otherwise stated. Air- and / or moisture- sensitive reactions were carried out under an atmosphere of argon.

1-(4',4'-Dimethyloxazolin-2'-yl)naphthalene (1). To a solution of 1-naphthoic acid (20.0 g, 116 mmol) in dichloromethane (300 ml) at room temperature oxalyl chloride (17.7 g, 139 mmol) and DMF (4 drops) were added. After stirring at room temperature for 5 hours, the mixture was concentrated to remove excess oxalyl chloride, redissolved in dichloromethane (400 ml), cooled down to 0 °C and treated with a solution of Et_3N (7.0 g, 69.6 mmol) and 2-amino-2-methyl-1-propanol (11.4 g, 128 mmol) in dichloromethane (30 ml). The mixture was allowed to warm to room temperature and stirred overnight. The

resulting solution was poured into 1N hydrochloric acid and extracted with dichloromethane (2x). The combined organic layers were washed with water, 2% $NaHCO_3$ aq. solution and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue (ca. 29 g) was dissolved in dichloromethane (500 ml), treated with thionyl chloride (27.6 g, 232 mmol) carefully (spontaneously boiling) and stirred for 4 hours at room temperature. The mixture was concentrated to remove excess thionyl chloride, diluted with ether (250 ml), and treated with 2N NaOH aqueous solution (250 ml). After stirring for 30 minutes, the mixture was treated with $NaHCO_3$ (powder, 40 g) and stirred overnight. The resulting heterogeneous mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated. Chromatography (20% EtOAc / hexane) and recrystallization (hexane-AcOEt) gave 1-(4',4'-dimethyloxazolin-2'-yl)naphthalene **(1)** (22.5 g, 86%) as a white solid (m.p. 47.0 ~ 49.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.48 (s, 6H), 4.16 (s, 2H), 7.40 ~ 7.65 (m, 3H), 7.86 (d, J = 8.3, 1H), 7.94 (d, J = 7.6, 1H), 8.04 (dd, J = 7.3, 1.3, 1H), 9.04 (d, J = 8.2, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.5 (q, 2C), 68.3 (s), 78.3(t), 124.6 (d), 125.0 (s), 126.0 (d), 126.3 (d), 127.2 (d), 128.3 (d), 128.7 (d), 131.1 (s), 131.6 (d), 133.6 (s), 161.9 (s); IR (KBr) 2980, 1645, 1590, 1510, 1290, 1190, 1120, 1000, 810, 780 cm^{-1}; EIMS *m / z* 225 (M^+), 210, 195, 182, 154; Anal. Calcd. for $C_{15}H_{15}N_1O_1$: C: 79.97; H: 6.71; N: 6.22; Found: C: 79.95; H: 6.81; N: 6.21.

Addition of lithium dibenzylamide to 1-(4',4'-dimethyloxazolin-2'-yl)naphthalene (1) (Table 1). To a stirred, cooled (-5 °C) solution of dibenzylamine (315 mg, 1.60 mmol) in THF (10 ml) was added *n*-butyllithium (1.72 M of hexane solution, 0.93 ml, 1.60 mmol). After stirring for 40 minutes at -5 °C, the mixture was cooled to -78 °C, treated with HMPA (1.72 g, 9.6 mmol), stirred to dissolve HMPA for 5 minutes and treated with naphthyloxazoline **1** (225 mg, 1.0 mmol) in THF (0.6 ml). The resulting dark red solution was maintained at between -78°C and -65 °C for 6 hours, then re-cooled to -78°C and treated with iodomethane (270 mg, 1.90 mmol). After stirring for 30 minutes at -78 °C, the mixture was allowed to warm to -10 °C over 3 hours. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water(2x) and brine, dried over $MgSO_4$ and concentrated. Column chromatography (hexane : ethyl acetate, 5 : 1) gave starting oxazoline (14 mg, 6.2%) and the adduct **2a (R_1 = R_2 = benzyl, E = Me)** (208 mg, 48%) as a white solid (m.p. 141.5 ~ 143.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.27 (s, 3H), 1.28 (s, 3H), 1.53 (s, 3H), 3.46 (d, J = 13.9, 2H), 3.75 (d, J = 7.9, 1H), 3.76 (d, J = 13.6, 2H), 3.82 (d, J = 7.9, 1H), 4.27 (bs, 1H), 6.02 (dd, J = 10.2, 2.0, 1H), 6.30 (dd, J = 10.2, 3.0, 1H), 7.15 ~ 7.36 (m, 9H), 7.40 (d, J = 7.3, 4H), 7.79 (d, J = 7.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q, 2C), 29.4 (q), 40.8 (s), 52.8 (d), 54.0 (t, 2C), 66.8 (s), 79.3 (t), 121.9 (d), 125.8 (d), 126.8 (d, 2C), 127.0 (d, 2C), 128.1 (d, 4C), 128.8 (d, 5C), 132.9 (d), 135.5 (s), 139.0 (s, 2C), 140.3 (s), 168.9 (s); IR (KBr) 2980, 1660, 1603, 1497, 1460, 1080, 970, 770, 742, 700 cm^{-1}; EIMS *m /z* 240 (M^+-NBn_2), 226, 196, 141; HRFABMS Calcd for $C_{30}H_{33}N_2O_1$: 437.2593; Found: 437.2582, and the adduct **3a (R_1 = R_2 = benzyl, E = Me)** (20 mg, 4.6 %) as a clear oil; ^{1}H NMR (270 MHz, $CDCl_3$) 1.25 (s, 3H), 1.26 (s, 3H), 1.67 (s, 3H), 3.44 (d, J = 13.2, 2H), 3.68 (d, J = 13.2, 2H), 3.73 (d, J = 8.2, 1H), 3.80 (d, J = 8.3, 1H), 4.39 (bs, 1H), 6.02 (dd, J = 10.6, 2.0, 1H), 6.29 (dd, J = 10.6, 3.3, 1H), 7.15 ~ 7.42 (m, 13H), 7.72 (dd, J = 7.3, 1.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.0 (q, 2C), 28.9 (q), 40.8 (s), 53.2 (d), 53.9 (t, 2C), 66.8 (s), 79.4 (t), 121.9 (d), 125.9 (d), 126.9 (d, 2C), 127.0 (d), 127.1 (d), 128.2 (d, 4C), 128.9 (d, 4C), 129.2 (d), 133.2 (d), 135.1 (s), 138.8 (s), 140.0 (s, 2C), 168.8 (s); IR (thin film) 2980, 1650, 1602, 1495, 1455, 1365, 1080, 740 cm^{-1}; FABMS *m/z* 437 ($M+H^+$), 369, 337, 277, 185; HRFABMS Calcd. for $C_{30}H_{33}N_2O_1$: 437.2593; Found: 437.2616, and the adduct **4a (R_1 = R_2 = benzyl, E = Me)** (16 mg, 3.6 %) as a white solid (m.p. 195.4 ~ 197.0 °C); ^{1}H

NMR (270 MHz, $CDCl_3$) 0.91 (d, J = 7.3, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 2.93 (m, 1H), 3.47 (d, J = 13.9, 2H), 3.58 (d, J = 13.9, 2H), 3.62 (bs, 1H), 3.97 (d, J = 7.9, 1H), 4.01 (d, J = 7.9, 1H), 6.82 (d, J = 6.3, 1H), 7.14 ~ 7.36 (m, 13H), 8.06 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 19.1 (q), 28.4 (q), 28.5 (q), 28.8 (d), 53.2 (t, 2C), 59.4 (d), 68.0 (s), 77.9 (t), 125.0 (s), 125.7 (d), 126.8 (d, 2C), 127.4 (d), 127.6 (d), 128.1 (d, 4C), 128.8 (d, 4C), 130.9 (d), 131.0 (s), 133.3 (s), 139.4 (d), 140.3 (s, 2C), 161.1 (s); IR (KBr) 2950, 1645, 1606, 1550, 1495, 1455, 775, 750, 700 cm^{-1}; EIMS *m/z* 436 (M^+), 394, 345, 317, 240; HRFABMS Calcd. for $C_{30}H_{33}N_2O_1$: 437.2593; Found: 437.2592.

The lithium dibenzylamide addition was repeated under various conditions as described in Table 1.

General procedure for the addition of lithium amide to naphthyloxazoline 1 followed by subsequent reaction with an electrophile. To a stirred, cooled (-5°C) solution of dialkylamine (1.2 ~ 1.6 equiv.) in THF (10 ml) *n*-butyllithium (1.2 ~ 1.6 equiv.) was added dropwise. The reaction mixture was stirred at -5°C for 30 minutes, then cooled to -78°C, treated with HMPA (2.4 ml), stirred for 5 min, and treated with 1-(4',4'-dimethyloxazolin-2'-yl)naphthalene (**1**) (225 mg, 1.0 mmol) in THF (0.6 ml) dropwise. The resulting dark-colored solution was stirred at between -65°C and -55°C for 6 hours, re-cooled to -78°C, and treated with an electrophile (1.4 ~ 1.9 equiv.). After stirring at -78°C for 1 hour, the mixture was allowed to warm to -10°C over 3 hours. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water (x 2) and brine, dried over $MgSO_4$ and concentrated. Silica gel column chromatography (hexane : ethyl acetate : dichloromethane) gave adducts, as shown in Table 2.

Adduct 2b (R_1 = R_2 = benzyl, E = allyl): a white solid (m.p. 109.0 ~ 112.0 °C); ^1H NMR (270 MHz, $CDCl_3$) 1.27 (s, 6H), 2.80 (m, 2H), 3.73 (d, J = 13.9, 2H), 3.76 (d, J = 7.9, 1H), 3.83 (d, J = 8.3, 1H), 4.22 (bs, 1H), 4.77 (dd, J = 10.2, 2.3, 1H), 4.84 (dd, J = 17.2, 2.0, 1H), 5.29 (m, 1H), 5.96 (dd, J = 10.2, 2.0, 1H), 6.41 (dd, J = 10.2, 3.3, 1H), 7.15 ~ 7.45 (m, 13H), 7.75 (bd, J = 6.9, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.2 (q, 2C), 44.4 (s), 45.3 (t), 53.0 (d), 54.0 (t, 2C), 66.9 (s), 79.1 (t), 117.8 (t), 123.5 (d), 125.8 (d), 126.8 (d, 2C), 126.9 (d), 127.1 (d), 128.2 (d, 4C), 128.8 (d, 5C), 130.9 (d), 133.4 (d), 136.7 (s), 136.9 (s), 140.4 (s, 2C), 168.2 (s); IR (KBr) 2930, 1655, 1495, 1455, 1365, 1200, 755, 700 cm^{-1}; EIMS *m /z* 462 (M^+), 421, 371, 329, 226; HRFABMS Calcd. for $C_{32}H_{35}N_2O_1$: 463.2749; Found: 463.2757.

Adduct 4b (R_1 = R_2 = benzyl, E = allyl): a white solid (m.p. 125.0 ~ 128.0 °C); ^1H NMR (270 MHz, $CDCl_3$) 1.37 (s, 3H), 1.39 (s, 3H), 1.81 (m, 1H), 2.07 (m, 1H), 2.86 (m, 1H), 3.47 (d, J = 13.9, 2H), 3.54 (d, J = 13.5, 2H), 3.75 (s, 1H), 3.96 (d, J = 7.9, 1H), 4.01 (d, J = 7.9, 1H), 4.83 (dd, J = 15.9, 1.3, 1H), 4.85 (d, J = 11.6, 1H), 5.60 (m, 1H), 6.84 (d, J = 6.3, 1H), 7.15 ~ 7.36 (m, 13H), 8.12 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.4 (q), 28.6 (q), 34.6 (d), 37.5 (t), 53.3 (t, 2C), 56.9 (d), 68.1 (s), 77.8 (t), 117.1 (t), 125.6 (s), 125.8 (d), 126.7 (d, 2C), 127.5 (d), 127.6 (d), 128.1 (d, 4C), 128.9 (d, 4C), 130.9 (d), 131.1 (s), 133.1 (s), 135.4 (d), 137.8 (d), 140.3 (s, 2C), 160.9 (s); IR (KBr) 2950, 1640, 1605, 1495, 1455, 1015, 770, 740, 700 cm^{-1}; HRFABMS Calcd. for $C_{32}H_{35}N_2O_1$: 463.2749; Found: 463.2744.

Adduct 2c (R_1 = R_2 = E = benzyl): a white solid (m.p. 136.0 ~ 138.0 °C); ^1H NMR (270 MHz, $CDCl_3$) 1.31 (s, 3H), 1.33 (s, 3H), 3.17 (bs, 1H), 3.27 (s, 2H), 3.34 (d, J = 13.9, 2H), 3.61 (d, J = 13.5, 2H), 3.83 (d, J = 7.9, 1H), 3.89 (d, J = 8.2, 2H), 5.96 (dd, J = 10.6, 2.3, 1H), 6.26 (dd, J = 10.6, 2.3, 1H), 6.53 (m, 2H), 6.79 (m, 3H), 7.12 ~ 7.31 (m, 12H), 7.50 (m, 4H), 7.68 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.2 (q, 2C), 46.2 (s), 46.9 (t), 52.7 (d), 53.9 (t, 2C), 67.0 (s), 79.1 (t), 125.0 (d), 125.87 (d), 125.93 (d), 126.6 (d, 2C),

126.7 (d, 2C), 126.8 (d), 126.9 (d), 127.8 (d), 128.0 (d, 4C), 128.6 (d, 4C), 129.6 (d), 130.5 (d, 2C), 136.0 (s), 136.6 (s), 137.7 (s), 140.0 (s, 2C), 140.3 (s), 168.3 (s); IR (KBr) 3050, 2950, 1650, 1540, 1495, 1455, 1200, 1020, 750, 700 cm^{-1}; EIMS *m /z* 421 (M^+-Bn), 316, 258, 226; Anal. Calcd. for $C_{36}H_{36}N_2O_1$: C: 84.34; H: 7.08; N: 5.46; Found: C: 84.56; H: 7.21; N: 5.44.

Adduct 2d (R_1 = benzyl, R_2 = Me, E = allyl): a white solid (m.p. 76.0 ~ 77.0 °C); ^1H NMR (270 MHz, $CDCl_3$) 1.28 (s, 3H), 1.29 (s, 3H), 2.22 (s, 3H), 2.78 (bdd, J = 14.2, 7.3, 1H), 2.86 (bdd, J = 14.2, 7.3, 1H), 3.50 (d, J = 13.2, 1H), 3.65 (d, J = 13.2, 1H), 3.79 (d, J = 7.9, 1H), 3.84 (d, J = 8.2, 1H), 4.29 (bs, 1H), 4.82 (bd, J = 9.9, 1H), 4.87 (bd, J = 17.2, 1H), 5.36 (ddt, J = 17.2, 9.9, 6.9, 1H), 5.95 (dd, J = 10.6, 2.0, 1H), 6.30 (dd, J = 10.6, 3.0, 1H), 7.16 ~ 7.41 (m, 8H),7.78 (dd, J = 7.3, 1.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q, 2C), 38.1 (q), 44.5 (s), 45.4 (t), 57.4 (t), 58.2 (d), 66.9 (s), 79.1 (t), 117.9 (t), 123.9 (d), 125.9 (d), 126.7 (d), 126.9 (d), 127.1 (d), 128.1 (d, 2C), 128.6 (d, 2C), 128.8 (d), 130.9 (d), 133.4 (d), 136.6 (s), 136.7 (s), 140.3 (s), 168.2 (s); IR (KBr) 2920, 1650, 1620, 1560, 1460, 1020, 820, 770, 745, 710 cm^{-1}; EIMS *m /z* 345 (M^+-allyl), 267, 226, 154; HRFABMS Calcd. for $C_{26}H_{31}N_2O_1$: 387.2436; Found: 387.2446; Anal. Calcd. for $C_{26}H_{30}N_2O_1$: C: 80.79; H: 7.82; N: 7.25; Found: C: 80.89; H: 7.95; N: 7.19.

Adduct 4d (R_1 = benzyl, R_2 = Me, E = allyl): a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 1.38 (s, 3H), 1.40 (s, 3H), 1.93 (m, 1H), 2.11 (s, 3H), 2.16 (m, 1H), 2.80 (m, 1H), 3.53 (s, 2H), 3.73 (bs, 1H), 3.97 (d, J = 7.9, 1H), 4.02 (d, J = 7.9, 1H), 4.97 (bd, J = 17.2, 1H), 4.99 (bd, J = 10.2, 1H), 5.74 (m, 1H), 6.84 (d, J = 5.6, 1H), 7.15 ~ 7.36 (m, 8H), 8.09 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.4 (q), 28.5 (q), 35.5 (d), 36.9 (t), 58.0 (t), 62.3 (d), 68.0 (s), 77.8 (t), 117.2 (t), 125.6 (s), 125.9 (d), 127.5 (d), 127.6 (d), 128.1 (d, 2C), 128.8 (d, 2C), 130.8 (d), 131.1 (s), 132.4 (s), 135.6 (d), 138.0 (d), 139.9 (s), 160.9 (s); IR (thin film) 2995, 1650, 1605, 1495, 1440, 1190, 1010, 740, 700 cm^{-1}; EIMS *m/z* 386 (M^+), 346, 266, 250; HRFABMS Calcd. for $C_{26}H_{31}N_2O_1$: 387.2436; Found: 387.2459.

Adduct 2e (R_1 = benzyl, R_2 = Me, E = benzyl): a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 1.33 (s, 3H), 1.35 (s, 3H), 2.07 (s, 3H), 3.23 (bs, 1H), 3.27 (d, J = 13.2, 1H), 3.33 (d, J = 7.6, 1H), 3.38 (d, J = 7.4, 1H), 3.52 (d, J = 13.5, 1H), 3.85 (d, J = 8.3, 1H), 3.90 (d, J = 8.3, 1H), 5.94 (dd, J = 10.6, 2.3, 1H), 6.16 (dd, J = 10.6, 2.6, 1H), 6.54 ~ 6.63 (m, 2H), 6.87~7.05 (m, 3H), 7.13~7.34 (m, 7H), 7.52 (m, 1H), 7.67 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.2 (q, 2C), 37.8 (q), 46.3 (s), 46.8 (t), 57.3 (t), 57.7 (d), 67.0 (s), 79.1 (t), 125.2 (d), 125.9 (d), 126.0 (d), 126.6 (d), 126.8 (d), 126.9 (d, 2C), 128.0 (d, 3C), 128.5 (d, 2C), 129.7 (d), 130.7 (d, 2C), 136.4 (s, 2C), 137.5 (s), 140.2 (s), 168.4 (s); IR (thin film) 2950, 1660, 1610, 1495, 1455, 1200, 1020, 760, 740, 700 cm^{-1}; HRFABMS Calcd. for $C_{30}H_{33}N_2O_1$: 437.2593; Found: 437.2591.

Adduct 2f (R_1 = R_2 = allyl, E = Me): a white solid (m.p. 77.0 ~ 79.0 °C); ^1H NMR (270 MHz, $CDCl_3$) 1.298 (s, 3H), 1.302 (s, 3H), 1.55 (s, 3H), 2.97 (dd, J = 14.2, 7.9, 2H), 3.24 (ddt, J = 14.2, 4.3, 2.3, 2H), 3.80 (d, J = 7.9, 1H), 3.86 (d, J = 7.9, 1H), 4.42 (bs, 1H), 5.07 (d, J = 10.2, 2H), 5.19 (d, J = 17.2, 2H), 5.83 (m, 2H), 5.93 (dd, J = 10.6, 2.0, 1H), 6.10 (dd, J = 10.6, 3.0, 1H), 7.17 ~ 7.36 (m, 3H), 7.73 (dd, J = 6.6, 2.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q, 2C), 29.3 (q), 40.8 (s), 53.0 (t, 2C), 53.8 (d), 66.9 (s), 79.3 (t), 116.4 (t, 2C), 122.7 (d), 125.7 (d), 126.7 (d), 126.9 (d), 128.7 (d), 132.4 (d), 135.8 (s), 137.6 (d, 2C), 138.9 (s), 169.0 (s); IR (KBr) 2950, 1650, 1560, 1540, 1505, 1420, 1200, 920, 765, 745 cm^{-1}; EIMS *m/z* 241, 226, 210, 141; HRFABMS Calcd. for $C_{22}H_{29}N_2O_1$: 337.2280; Found: 337.2264: Anal. Calcd. for $C_{22}H_{28}N_2O_1$: C: 78.53; H: 8.39; N: 8.33; Found: C: 78.58; H: 8.50; N: 8.42.

Adduct 3f (R_1 = R_2 = allyl, E = Me): a white solid (m.p. 61.0 ~ 63.0 °C); ^1H NMR (270 MHz, $CDCl_3$) 1.26 (s, 3H), 1.28 (s, 3H), 1.66 (s, 3H), 2.96 (dd, J = 14.2, 8.3, 2H), 3.17

(dt, J = 14.2, 2.3, 2H), 3.77 (d, J = 8.3, 1H), 3.83 (d, J = 8.3, 1H), 4.55 (bs, 1H), 5.07 (bd, J = 9.9, 2H), 5.18 (bd, J = 17.2, 2H), 5.82 (m, 2H), 5.93 (dd, J = 10.2, 1.7, 1H), 6.10 (dd, J = 10.2, 3.0, 1H), 7.16 ~ 7.36 (m, 3H), 7.67 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.0 (q, 2C), 28.7 (q), 40.7 (s), 53.0 (t, 2C), 54.3 (d), 66.8 (s), 79.4 (t), 116.7 (t, 2C), 122.7 (d), 125.9 (d), 126.9 (d), 127.0 (d), 129.1 (d), 132.7 (d), 135.4 (s), 137.3 (d, 2C), 138.6 (s), 168.9 (s); IR (KBr) 2990, 1650, 1490, 1450, 1360, 1280, 1085, 920, 760, 720 cm^{-1}; EIMS *m /z* ; 321 (M^+-Me), 295, 240, 237; HRFABMS Calcd. for $C_{22}H_{29}N_2O_1$: 337.2280; Found: 337.2273.

Adduct 4f (R_1 = R_2 = allyl, E = Me): a white solid (m.p. 83.0 ~ 85.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.02 (d, J = 7.3, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 2.74 (m, 1H), 3.05 (dd, J = 14.2, 7.3, 2H), 3.18 (d, J = 14.2, 5.3, 2H), 3.77 (d, J = 4.0, 1H), 3.99 (d, J = 8.3, 1H), 4.02 (d, J = 8.2, 1H), 5.07 (d, J = 11.2, 2H), 5.14 (d, J = 17.2, 2H), 5.78 (m, 2H), 6.76 (d, J = 5.6, 1H), 7.20 ~ 7.38 (m, 3H), 8.02 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 18.6 (q), 28.4 (q), 28.5 (q), 30.4 (d), 52.8 (t, 2C), 61.1 (d), 67.9 (s), 77.9 (t), 116.7 (t, 2C), 125.1 (s), 125.8 (d), 127.2 (d), 127.5 (d), 129.9 (d), 131.3 (s), 134.3 (s), 137.4 (d, 2C), 140.0 (d), 161.0 (s); IR (KBr) 2980, 1645, 1605, 1560, 1120, 1000, 775 cm^{-1}; EIMS *m/z* 336 (M^+), 295, 267, 240; HRFABMS Calcd. for $C_{22}H_{29}N_2O_1$: 337.2280; Found: 337.2307.

Adduct 2g (R_1 = R_2 = E = allyl): a white solid (m.p. 74.0 ~ 76.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.29 (s, 3H), 1.30 (s, 3H), 2.80 (m, 2H), 2.97 (dd, J = 14.5, 8.3, 2H), 3.22 (ddt, J = 14.5, 4.3, 1.7, 2H), 3.80 (d, J = 8.3, 1H), 3.85 (d, J = 8.3, 1H), 4.35 (t, J = 2.3, 1H), 4.84 (bd, J = 9.9, 1H), 4.86 (bd, J = 17.2, 1H), 5.07 (bd, J = 8.2, 2H), 5.18 (bd, J = 17.2, 2H), 5.36 (ddt, J = 17.2, 9.9, 6.9, 1H), 5.82 (m, 2H), 5.88 (dd, J = 10.2, 2.0, 1H), 6.20 (dd, J = 10.2, 2.6, 1H), 7.17 ~ 7.29 (m, 2H), 7.34 (m, 1H), 7.71 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q, 2C), 44.5 (s), 45.4 (t), 53.0 (t, 2C), 54.0 (d), 66.9 (s), 79.1 (t), 116.4 (t, 2C), 117.9 (t), 124.3 (d), 125.8 (d), 126.8 (d), 126.9 (d), 128.5 (d), 130.2 (d), 133.3 (d), 136.7 (s), 137.0 (s), 137.6 (d, 2C), 168.2 (s); IR (KBr) 2930, 1650, 1542, 1440, 1200, 920, 765 cm^{-1}; EIMS *m /z* 362 (M^+), 321, 266, 226, 210; Anal. Calcd. for $C_{24}H_{30}N_2O_1$: C: 79.52; H: 8.34; N: 7.73; Found: C: 79.54; H: 8.42; N: 7.77.

Adduct 4g (R_1 = R_2 = E = allyl): a clear oil; ^{1}H NMR (270 MHz, $CDCl_3$) 1.38 (s, 3H), 1.40 (s, 3H), 2.00 (m, 1H), 2.12 (m, 1H), 2.71 (m, 1H), 2.97 ~ 3.17 (m, 4H), 3.86 (d, J = 2.6, 1H), 3.98 (d, J = 7.9, 1H), 4.02 (d, J = 7.9, 1H), 4.90 ~ 5.22 (m, 6H), 5.65 ~ 5.87 (m, 3H), 6.81 (d, J = 5.9, 1H), 7.17 ~ 7.33 (m, 3H), 8.08 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.4 (q), 28.5 (q), 35.5 (d), 37.0 (t), 52.8 (t, 2C), 58.6 (d), 68.0 (s), 77.8 (t), 116.7 (t, 2C), 117.2(t), 125.6 (s), 125.9 (d), 127.4 (d), 127.5 (d), 130.4 (d), 131.2 (s), 133.7 (s), 135.7 (d), 137.4 (d, 2C), 138.0 (d), 160.8 (s); IR (thin film) 3080, 2990, 1650, 1610, 1490, 1450, 1110, 1020, 775, 745 cm^{-1}; EIMS *m/z* 362 (M^+), 322, 266, 226, 170; HRFABMS Calcd. for $C_{24}H_{31}N_2O_1$: 363.2436; Found: 363.2406.

Adduct 2h (R_1 = R_2 = allyl, E = prenyl): a clear oil; ^{1}H NMR (270 MHz, $CDCl_3$) 1.30 (s, 3H), 1.32 (s, 3H), 1.37 (s, 3H), 1.50 (s, 3H), 2.71 (d, J = 7.3, 2H), 2.97 (dd, J = 14.2, 8.3, 2H), 3.21 (dt, J = 14.2, 4.3, 2.0, 2H), 3.81 (d, J = 7.9, 1H), 3.86 (d, J = 8.2, 1H), 4.33 (s, 1H), 4.74 (t, J = 7.3, 1H), 5.07 (d, J = 10.2, 2H),5.19 (d, J = 17.2, 2H), 5.82 (m, 2H), 5.90 (dd, J = 10.2, 2.0, 1H), 6.18 (dd, J = 10.2, 3.0, 1H), 7.16 ~ 7.26 (m, 2H), 7.37 (dd, J = 6.6, 2.3, 1H), 7.73 (dd, J = 6.9, 2.0, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 17.8 (q), 25.9 (q), 28.1 (q), 28.2 (q), 39.5 (t), 45.1 (s), 53.0 (t, 2C), 54.1 (d), 66.9 (s), 79.0 (t), 116.4 (t, 2C), 118.9 (d), 124.3 (d), 125.9 (d), 126.6 (d), 126.8 (d), 128.1 (d), 130.4 (d), 134.3 (d), 137.3 (s, 2C), 137.6 (d, 2C), 168.5 (s); IR (thin film) 2995, 1655, 1445, 1275, 1200, 1000, 920, 760 cm^{-1}; HRFABMS Calcd. for $C_{26}H_{35}N_2O_1$: 391.2749; Found: 391.2758.

Adduct 4h (R_1 = R_2 = allyl, E = prenyl): a white solid (m.p. 60.0 ~ 62.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.38 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.68 (s, 3H), 1.86 (m, 1H),

2.03 (m, 1H), 2.62 (m, 1H), 3.03 (m, 4H), 3.83 (d, J = 1.7, 1H), 3.98 (d, J = 7.9, 1H), 4.02 (d, J = 7.9, 1H), 5.00 ~ 5.18 (m, 5H), 5.74 (m, 2H), 6.83 (d, J = 6.3, 1H), 7.21 ~ 7.31 (m, 3H), 8.08 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 17.8 (q), 25.8 (q), 28.3 (q), 28.5 (q), 30.9 (t), 36.1 (d), 52.6 (t, 2C), 57.7 (d), 68.0 (s), 116.5 (t, 2C), 121.5(d), 125.3 (s), 125.7 (d), 127.3 (d), 127.4 (d), 130.7 (d), 131.2 (s), 133.7 (s), 134.7 (s), 137.5 (d, 2C), 138.7 (d), 161.0 (s); IR (KBr) 2980, 1650, 1605, 1440, 1290, 1010, 770 cm^{-1}; HRFABMS Calcd. for $C_{26}H_{34}N_2O_1$: 391.2749; Found: 391.2747.

Adduct 2i (R_1 = R_2 = allyl, E = benzyl): a white solid (m.p. 78.0 ~ 80.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.34 (s, 3H), 1.36 (s, 3H), 2.83 (dd, J = 14.5, 8.2, 2H), 3.08 (ddd, J = 14.5, 2.3, 2.0, 2H), 3.25 (d, J = 13.2, 1H), 3.28 (bs, 1H), 3.34 (d, J = 13.2, 1H), 3.87 (d, J = 8.2, 1H), 3.91 (d, J = 8.3, 1H), 4.97 (d, J = 10.2, 2H), 5.05 (d, J = 17.2, 2H), 5.67 (m, 2H), 5.88 (dd, J = 10.6, 2.3, 1H), 6.05 (dd, J = 10.6, 2.5, 1H), 6.61 (d, J = 6.9, 2H), 6.90 ~ 7.07 (m, 3H), 7.17 ~ 7.32 (m, 2H), 7.49 (dd, J = 7.3, 1.3, 1H), 7.57 (d, J = 7.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.3 (q, 2C), 46.4 (s), 46.8 (t), 52.9 (t, 2C), 53.6 (d), 67.0 (s), 79.2 (t), 116.4 (t, 2C), 125.88 (d), 125.93 (d), 126.0 (d), 126.7 (d), 126.8 (d, 2C), 126.9 (d), 127.7 (d), 129.0 (d), 130.8 (d, 2C), 136.4 (s), 136.5 (s), 137.2 (d, 2C), 138.2 (s), 168.5 (s); IR (KBr) 2980, 1650, 1540, 1470, 1020, 765, 738, 705 cm^{-1}; EIMS *m /z* 316 (M^+-diallylamino), 226, 210, 154; HRFABMS Calcd. for $C_{28}H_{33}N_2O_1$: 413.2593; Found: 413.2620; Anal. Calcd. for $C_{28}H_{32}N_2O_1$: C: 81.51; H: 7.82; N: 6.79; Found: C: 81.29; H: 7.90; N: 6.67.

1-(2'-Oxazolinyl)naphthalene (5). To a solution of 1-naphthoic acid (5.0 g, 29.0 mmol) in dichloromethane (100 ml) at room temperature oxalyl chloride (5.53 g, 43.6 mmol) and DMF (2 drops) were added. After stirring at room temperature for 4 hours, the mixture was concentrated to remove excess oxalyl chloride, redissolved in dichloromethane (150 ml), cooled down to 0 °C and treated with a solution of Et_3N (3.23 g, 31.9 mmol) and 2-aminoethanol (1.95 g, 31.9 mmol) in dichloromethane (5.0 ml). The mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was poured into 1N hydrochloric acid and extracted with dichloromethane (2x). The combined organic layers were washed with water, 2 % $NaHCO_3$ aq. solution and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue (ca. 7.0 g) was dissolved in dichloromethane (150 ml), treated with thionyl chloride (6.91 g, 58.1 mmol) carefully (spontaneously boiling) and stirred for 48 hours at room temperature. The mixture was concentrated to remove excess thionyl chloride, diluted with acetonitrile (160 ml), treated with aqueous potassium carbonate solution (20 g in 90 ml of H_2O), refluxed for 24 hours and concentrated to remove acetonitrile. The resulting heterogeneous mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated. Silica gel column chromatography (25% EtOAc / hexane) gave 1-(2'-oxazolinyl) naphthalene (**5**) (4.64 g, 81 %) as a white solid (m.p. 44.0 ~ 45.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 4.19 (m, 2H), 4.42 (m, 2H), 7.40 ~ 7.65 (m, 3H), 7.85 (dd, J = 7.9, 1.3, 1H), 7.93 (d, J = 8.3, 1H), 8.08 (dd, J = 7.3, 1.3, 1H), 9.13 (dd, J = 9.2, 1.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 55.7 (t), 66.5 (t), 124.5 (s), 124.6 (d), 126.0 (d), 126.3 (d), 127.2 (d), 128.4 (d), 128.9 (d), 131.1 (s), 131.8 (d), 133.6 (s), 164.3 (s); IR (KBr) 2950, 1640, 1490, 1505, 1320, 1120, 1000, 810, 780 cm^{-1}; HRFABMS Calcd. for $C_{13}H_{12}N_1O_1$: 198.0919; Found: 198.0914.

Addition of lithium *N*-methyl-*N*-allylamide to naphthyloxazoline 1. The reaction was conducted under the general conditions. ^{1}H NMR (270 MHz, $CDCl_3$) of the crude products showed that the ratio of **2k**, **3k**, **4k** and **6k** was 26 : 13 : 4 : 57. Silica gel column chromatography (hexane : ethyl acetate : dichloromethane) gave **2k** and **3k** as a mixture (94 mg, 30%) as a clear oil; IR (thin film) 2950, 1655, 1455, 1365, 1280, 1200,

1080, 765, 745 cm^{-1}; HRFABMS Calcd. for $C_{20}H_{27}N_2O_1$: 311.2124; Found: 311.2112; 1,6-*trans* adduct **2k** (major isomer) [^{1}H NMR (270 MHz, $CDCl_3$) 1.29 (s, 3H), 1.30 (s, 3H), 1.57 (s, 3H), 2.19 (s, 3H), 3.03 ~ 3.20 (m, 2H), 3.81 (d, J = 8.3, 1H), 3.85 (d, J = 8.3, 1H), 4.34 (bs, 1H), 5.09 (bd, J = 9.9, 1H), 5.20 (dd, J = 17.2, 1.7, 1H), 5.87 (m, 1H), 5.98 (dd, J = 10.6, 1.0, 1H), 6.08 (dd, J = 10.6, 3.0, 1H), 7.18 ~ 7.37 (m, 3H), 7.67 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q, 2C), 29.3 (q), 37.6 (q), 40.8 (s), 56.7 (t), 57.5 (d), 66.8 (s), 79.3 (t), 116.5 (t), 122.2 (d), 125.9 (d), 126.8 (d), 126.9 (d), 128.7 (d), 133.0 (d), 135.3 (s), 137.2 (d), 138.8 (s), 168.9 (s)]; 1,6-*cis* adduct **3k** (minor isomer) [^{1}H NMR (270 MHz, $CDCl_3$ extract) 1.27 (s, 3H), 1.29 (s, 3H), 1.66 (s, 3H), 2.13 (s, 3H), 4.47 (bs, 1H), 5.11 (dd, J = 10.2, 3.0, 1H), 7.62 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.0 (q, 2C), 28.5 (q), 37.2 (q), 40.8 (s), 56.9 (t), 57.8 (d), 66.8 (s), 79.3 (t), 116.8 (t), 122.1 (d), 125.8 (d), 126.9 (d), 127.0 (d), 129.1 (d), 133.3 (d), 134.8 (s), 136.9 (d), 138.6 (s), 168.9 (s)] and **4k** as a clear oil (8.2 mg, 2.6 %) [^{1}H NMR (270 MHz, $CDCl_3$) 1.00 (d, J = 7.3, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 2.11 (s, 3H), 2.76 (m, 1H), 3.10 (d, J = 6.3, 2H), 3.59 (d, J = 2.3, 1H), 3.99 (d, J = 8.3, 1H), 4.03 (d, J = 7.9, 1H), 5.11 (d, J = 9.2, 1H), 5.16 (d, J = 15.8, 1H), 5.84 (m, 1H), 6.80 (d, J = 5.9, 1H), 7.18 ~ 7.35 (m, 3H), 8.04 (d, J = 7.9, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 18.7 (q), 28.8 (q), 29.0 (q), 31.1 (q), 38.0 (d), 57.9 (t), 65.3 (d), 68.4 (s), 78.4 (t), 117.6 (t), 125.5 (s), 126.3 (d), 127.9 (d), 128.0 (d), 131.0 (d), 131.6 (s), 132.8 (s), 137.3 (d), 140.2 (d), 161.5 (s); IR (thin film) 2950, 1650, 1605, 1450, 1020, 1000, 775 cm^{-1}; HRFABMS Calcd. for $C_{20}H_{27}N_2O_1$: 311.2124; Found: 311.2143] and **6k** as a clear oil (149 mg, 48 %); ^{1}H NMR (270 MHz, $CDCl_3$) 1.35 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 2.03 (s, 3H), 3.04 (d, J = 6.6, 2H), 3.45 (d, J = 5.6, 1H), 3.94 (d, J = 7.6, 1H), 3.98 (d, J = 7.9, 1H), 5.02 (dd, J = 11.2, 1.0, 1H), 5.07 (dd, J = 17.8, 1.7, 1H), 5.73 (m, 1H), 5.84 (dd, J = 9.9, 5.3, 1H), 6.69 (d, J = 9.9, 1H), 7.06 (dd, J = 6.9, 2.0, 1H), 7.10 ~ 7.24 (m, 2H), 7.41 (dd, J = 6.9, 1.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q), 28.3 (q), 29.0 (q), 36.9 (q), 45.3 (s), 57.8 (t), 65.4 (d), 66.9 (s), 78.6 (t), 116.2 (t), 121.2 (d), 126.3 (d), 127.2 (d), 127.5 (d), 127.7 (d), 129.3 (d), 130.9 (s), 137.4 (d), 138.9 (s), 168.2 (s); IR (thin film) 2995, 1655, 1455, 1362, 1040, 790, 755 cm^{-1}; HRFABMS Calcd. for $C_{20}H_{27}N_2O_1$: 311.2124; Found: 311.2104.

Addition of lithium *N*-methyl-*N*-phenethylamide to naphthyloxazoline 1. The reaction was conducted according to the general procedure, but the details were described in Table 3.

Adduct 6l: a white solid (m.p. 73.0 ~ 75.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) 1.29 (s, 3H), 1.36 (s, 3H), 2.06 (s, 3H), 2.36 (dd, J = 13.2, 7.6, 1H), 2.57 ~ 2.87 (m, 5H), 3.55 (d, J = 5.3, 1H), 3.90 (s, 2H), 4.75 (dt, J = 16.8, 1.0, 1H), 4.88 (dd, J = 10.2, 2.3, 1H), 5.53 (m, 1H), 5.81 (dd, J = 9.9, 5.3, 1H), 6.67 (d, J = 9.9, 1H), 7.00 ~ 7.29 (m, 8H), 7.61 (dd, J = 6.6, 2.3, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.2 (q), 28.6 (q), 35.4 (t), 36.2 (q), 44.0 (t), 49.3 (s), 57.9 (t), 66.0 (d), 67.3 (s), 78.2 (t), 117.8 (t), 121.5 (d), 125.8 (d), 126.4 (d), 126.6 (d), 127.1 (d), 128.2 (d, 2C), 128.6 (d, 2C), 129.6 (d), 131.3 (s), 134.3 (d), 135.3 (s), 140.5 (s), 166.2 (s); IR (KBr) 2980, 1655, 1635, 1460, 1350, 1200, 1035, 790, 755, 705 cm^{-1}; EIMS *m /z* 400 (M^+), 360, 309, 266, 226; HRFABMS Calcd. for $C_{27}H_{33}N_2O_1$: 401.2593; Found: 401.2594.

Adduct 2l: a clear oil; ^{1}H NMR (270 MHz, $CDCl_3$) 1.26 (s, 3H), 1.29 (s, 3H), 2.28 (s, 3H), 2.63 ~ 2.87 (m, 6H), 3.75 (d, J = 8.3, 1H), 3.80 (d, J = 8.3, 1H), 4.25 (t, J = 2.0, 1H), 4.78 ~ 4.93 (m, 2H), 5.35 (m, 1H), 5.88 (dd, J = 10.6, 2.0, 1H), 6.18 (dd, J = 10.6, 3.0, 1H), 7.11 ~ 7.29 (m, 7H), 7.35 (m, 1H), 7.52 (m, 1H), ; ^{13}C NMR (67.8 MHz, $CDCl_3$) 28.1 (q), 28.2 (q), 35.3 (t), 38.1 (q), 44.5 (s), 45.4 (t), 55.5 (t), 59.0 (d), 66.9 (s), 79.0 (t), 117.9 (t), 124.3 (d), 125.7 (d), 125.9 (d), 126.8 (d), 127.0 (d), 128.1 (d, 2C), 128.8 (d, 3C), 130.8 (d), 133.4 (d), 136.5 (s, 2C), 140.8 (s), 168.3 (s); IR (thin film) 2950, 1655, 1605, 1500,

1455, 1300, 1020, 765, 750, 700 cm^{-1}; HRFABMS Calcd. for $C_{27}H_{33}N_2O_1$: 401.2593; Found: 401.2598.

Addition of lithium di-*n*-propylamide to naphthyloxazoline 1. The reaction was conducted under the general conditions. ^1H NMR (270 MHz, $CDCl_3$) of the crude products showed that the ratio of **2m**, **3m** and **4m** was 74 : 22 : 4. Silica gel column chromatography (hexane : ethyl acetate : dichloromethane) gave starting oxazoline **1** (25 mg, 11 %), and **2m** and **3m** as a mixture (241 mg, 71 %) as a clear oil; IR (thin film) 2980, 1655, 1490, 1460, 1365, 1280, 1200, 1080, 760, 745 cm^{-1}; HRFABMS Calcd. for $C_{22}H_{33}N_2O_1$: 341.2593; Found: 341.2601; 1,6-*trans* adduct **2m** (major isomer) [^1H NMR (270 MHz, $CDCl_3$) 0.83 (t, J = 7.3, 6H), 1.31 (s, 3H), 1.32 (s, 3H), 1.44 (m, 4H), 1.55 (s, 3H), 2.43 (t, J = 7.6, 4H), 3.81 (d, J = 8.3, 1H), 3.87 (d, J = 8.3, 1H), 4.30 (bs, 1H), 5.93 (dd, J = 10.2, 2.0, 1H), 6.11 (dd, J = 10.2, 2.6, 1H), 7.16 ~ 7.34 (m, 3H), 7.74 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 11.8 (q, 2C), 22.2 (t, 2C), 28.2 (q, 2C), 29.3 (q), 40.9 (s), 52.8 (t, 2C), 55.4 (d), 66.9 (s), 79.2 (t), 123.9 (d), 125.6 (d), 126.5 (d), 126.7 (d), 129.0 (d), 131.8 (d), 136.5 (s), 138.7 (s), 169.2 (s)]; 1,6-*cis* adduct **3m** (minor isomer) [^1H NMR (270 MHz, $CDCl_3$ extract) 0.83 (t, J = 7.3, 6H), 1.26 (s, 3H), 1.28 (s, 3H), 1.66 (s, 3H), 4.43 (bs, 1H), 5.89 (dd, J = 10.2, 2.0, 1H), 6.11 (dd, J = 10.2, 2.6, 1H), 7.68 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 11.8 (q, 2C), 22.1 (t, 2C), 28.0 (q, 2C), 28.7 (q), 40.0 (s), 52.6 (t, 2C), 55.7 (d), 66.8 (s), 79.3 (t), 123.7 (d), 125.8 (d), 126.6 (d), 126.7 (d), 129.4 (d), 132.1 (d), 136.0 (s), 138.3 (s), 169.0 (s)] and **4m** as a clear oil (8.5 mg, 2.5 %); ^1H NMR (270 MHz, $CDCl_3$) 0.80 (t, J = 7.3, 6H), 1.09 (d, J = 7.3, 3H), 1.39 (s, 6H), 1.41 (m, 4H), 2.47 (t, J = 7.6, 4H), 2.73 (m, 1H), 3.67 (d, J = 6.8, 1H), 4.01 (s, 2H), 6.73 (d, J = 4.6, 1H), 7.16 ~ 7.30 (m, 2H), 7.40 (m, 1H), 7.95 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 11.8 (q, 2C), 19.3 (q), 22.6 (t, 2C), 28.4 (q, 2C), 31.3 (d), 53.0 (t, 2C), 64.0 (d), 67.9 (s), 78.0 (t), 125.3 (s), 125.8 (d), 126.9 (d), 127.4 (d), 129.1 (d), 131.6 (s), 136.1 (s), 140.7 (d), 161.2 (s); IR (thin film) 2980, 1650, 1455, 1020, 1000, 775 cm^{-1}; HRFABMS Calcd. for $C_{22}H_{33}N_2O_1$: 341.2593; Found: 341.2611.

Amide ester 7f. Amino adduct **2f** (240 mg, 0.71 mmol) was treated with 1N hydrochloric acid (4.0 ml) at room temperature and stirred until **2f** disappeared (ca. 6 hours). The mixture was diluted with THF (6.0 ml), cooled down to 0°C, and treated with 2N sodium hydroxide solution (3.5 ml) and acetic anhydride (291 mg, 2.85 mmol). The resulting heterogeneous solution was warmed to room temperature and continuously stirred vigorously for 3 hours. The mixture was then poured into 3% sodium bicarbonate solution, extracted with dichloromethane, dried over $MgSO_4$ and concentrated. Silica gel column chromatography (60% ethyl acetate / hexane) gave amide ester **7f** (273 mg, 97 %) as a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 1.13 (s, 3H), 1.18 (s, 3H), 1.54 (s, 3H), 1.64 (s, 3H), 2.96 (dd, J = 14.2, 8.3, 2H), 3.25 (m, 2H), 3.96 (d, J = 11.2, 1H), 4.26 (d, J = 11.2, 1H), 4.45 (bs, 1H), 5.04 (bs, 1H, NH), 5.11 (d, J = 9.9, 2H), 5.21 (d, J = 17.2, 2H), 5.82 (m, 2H), 5.95 (dd, J = 10.6, 2.0, 1H), 6.09 (dd, J = 10.6, 2.9, 1H), 7.10 ~ 7.32 (m, 3H), 7.73 (dd, J = 6.6, 2.0, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 23.6 (q), 24.0 (q), 24.4 (q), 28.3 (q), 47.2 (s), 53.0 (t), 53.2 (t), 53.7 (d), 69.7 (t), 117.0 (t, 2C), 122.7 (d), 125.9 (d), 126.95 (d), 127.04 (d), 129.0 (d), 131.1 (d), 135.5 (s), 137.3 (d, 2C), 138.2 (s), 169.5 (s) 174.8 (s); IR (thin film) 3300, 2980, 1738, 1660, 1555, 1455, 1220, 1100, 920, 755 cm^{-1}; HRFABMS Calcd. for $C_{24}H_{33}N_2O_3$: 397.2492; Found: 397.2520.

Ethyl ester 8f. To stirred ethanol (25 ml) was added a piece of metallic sodium (50 mg, 2.2 mmol). After the metallic sodium disappeared, amide ester **7g** (300 mg, 0.76 mmol) in ethanol (5 ml) was added in one shot and the mixture was refluxed for 4 hours. The resulting mixture was cooled to room temperature, acidified with acetic acid (0.15 ml), and concentrated to remove excess AcOH (xylene displacement x2). The residue was treated

with Et_3N (0.3 ml) and purified directly by silica gel column chromatography (20% ethyl acetate / hexane) to yield methyl ester **8f** (224 mg, 95%) as a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 1.09 (t, J = 7.3, 3H), 1.54 (s, 3H), 2.96 (dd, J = 14.5, 8.3, 2H), 3.25 (ddd, J = 14.5, 4.3, 2.3, 2H), 4.05 (m, 2H), 4.44 (bs, 1H), 5.07 (bd, J = 10.2, 2H), 5.18 (bd, J = 17.2, 2H), 5.82 (m, 2H), 5.93 (dd, J = 10.2, 1.7, 1H), 6.07 (dd, J = 10.2, 3.0, 1H), 7.16 ~ 7.30 (m, 3H), 7.67 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 13.9 (q), 28.1 (q), 46.9 (s), 53.1 (t, 2C), 53.9 (d), 61.1 (t), 116.5 (t, 2C), 122.5 (d), 126.0 (d), 126.8 (d), 127.0 (d), 129.1 (d), 131.8 (d), 135.7(s), 137.6 (d, 2C), 138.4 (s), 174.8 (s); IR (thin film) 2980, 1738, 1640, 1495, 1450, 1230, 1100, 920, 755 cm^{-1}; HRFABMS Calcd. for $C_{20}H_{26}N_1O_2$: 312.1963; Found: 312.1960.

δ-Amino acid methyl ester 9f. A solution of **8f** (120 mg, 0.39 mmol) and Wilkinson catalyst (20 mg, 22 mmol) in MeCN-H_2O (84 : 16, 15 ml) was refluxed for 90 minutes according to Ganem's procedure.[17] The resulting mixture was concentrated and purified directly by silica gel column chromatography (20 % ethanol / ethyl acetate) to give d-amino acid methyl ester **9f** (80 mg, 86 %) as a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 1.15 (t, J = 7.3, 3H), 1.61 (s, 3H), 1.85 (bs, 2H, $N\underline{H}_2$), 4.08 (m, 2H), 4.36 (d, J = 4.0, 1H), 5.82 (dd, J = 9.9, 1.0, 1H), 6.13 (dd, J = 9.9, 4.3, 1H), 7.20 ~ 7.37 (m, 3H), 7.46 (dd, J = 7.9, 1.7, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 13.9 (q), 26.5 (q), 47.0 (s), 48.3 (d), 61.3 (t), 126.3 (d), 127.0 (d), 127.6 (d), 128.3 (d), 129.8 (d), 130.7 (d), 137.1 (s), 138.7 (s), 174.4 (s); IR (thin film) 2980, 1735, 1230, 1100, 760 cm^{-1}; HRFABMS Calcd. for $C_{14}H_{18}N_1O_2$: 232.1337; Found: 232.1329.

Amide ester 7g. Amino adduct **2g** (2.5 g, 6.9 mmol) was treated with 2N hydrochloric acid (15 ml) at room temperature and stirred until **2g** disappeared (ca. 6 hours). The mixture was diluted with THF (30 ml), cooled to 0°C, and treated with 2N sodium hydroxide solution (30 ml) and acetic anhydride (2.82 g, 27.6 mmol). The resulting heterogeneous solution was warmed to room temperature and continuously stirred vigorously for 3 hours. The mixture was then poured into 3% sodium bicarbonate solution, extracted with dichloromethane, dried over $MgSO_4$ and concentrated. Silica gel column chromatography (60% ethyl acetate / hexane) gave amide ester **7g** (2.9 g, 99%) as a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 1.13 (s, 3H), 1.18 (s, 3H), 1.64 (s, 3H), 2.76 (d, J = 7.3, 2H), 2.96 (dd, J = 14.2, 8.3, 2H), 3.23 (m, 2H), 3.99 (d, J = 10.9, 1H), 4.27 (d, J = 11.2, 1H), 4.37 (t, J = 2.3, 1H), 4.87 (bd, J = 11.9, 1H), 4.88 (bd, J = 15.5, 1H), 5.04 (bs, 1H, N<u>H</u>), 5.11 (bd, J = 10.2, 2H), 5.20 (dd, J = 17.2, 0.7, 2H), 5.38 (m, 1H), 5.81 (m, 2H), 5.88 (dd, J = 10.5, 2.0, 1H), 6.18 (dd, J = 10.5, 3.0, 1H), 7.15 ~ 7.31 (m, 3H), 7.72 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 23.7 (q), 23.99 (q), 24.05 (q), 44.4 (t), 50.8 (s), 53.0 (s), 53.1 (t, 2C), 53.8 (d), 69.6 (t), 117.0 (t, 2C), 118.3 (t), 124.4 (d), 125.8 (d), 127.0 (d), 127.1 (d), 128.8 (d), 128.9 (d), 133.0 (d), 136.0 (s), 136.7 (s), 137.3 (d, 2C), 169.5 (s) 174.0 (s); IR (thin film) 3320, 3090, 2990, 1740, 1650, 1550, 1370, 1200, 920, 750 cm^{-1}; EIMS *m /z* 422 (M^+), 381, 264, 250, 195; HRFABMS Calcd. for $C_{26}H_{35}N_2O_3$: 423.2648; Found: 423.2635.

Methyl ester 8g. To stirred methanol (130 ml) was added a piece of metallic sodium (300 mg, 13 mmol). After the metallic sodium disappeared, amide ester **7g** (2.9 g, 6.8 mmol) in methanol (20 ml) was added in one shot and the mixture was refluxed for 4 hours. The resulting mixture was cooled down to room temperature, acidified with acetic acid (2 ml), and concentrated to remove excess AcOH (xylene displacement x2). The residue was treated with Et3N (2 ml), and purified directly by silica gel column chromatography (20% ethyl acetate / hexane) and gave methyl ester **8g** (2.14 g, 97%) as a clear oil; ^1H NMR (270 MHz, $CDCl_3$) 2.78 (d, J = 6.9, 2H), 2.97 (dd, J = 14.5, 7.9, 2H), 3.22 (ddt, J = 14.5, 4.3, 2.0, 2H), 3.62 (s, 3H), 4.37 (t, J = 2.3, 1H), 4.88 (bd, J = 9.9, 1H), 4.89 (bd, J = 17.2, 1H),

5.07 (bd, J = 9.9, 2H), 5.18 (bd, J = 16.2, 2H), 5.37 (ddt, J = 17.2, 9.9, 7.3, 1H), 5.83 (m, 2H), 5.89 (dd, J = 10.6, 2.0, 1H), 6.18 (dd, J = 10.2, 3.0, 1H), 7.16 ~ 7.32 (m, 3H), 7.69 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 44.6 (t), 50.6 (s), 52.5 (q), 53.0 (t, 2C), 54.0 (s), 116.5 (t, 2C), 118.2 (t), 124.4 (d), 125.9 (d), 126.97 (d), 127.01 (d), 128.8 (d), 129.4 (d), 133.2 (d), 136.0 (s), 136.9 (s), 137.5 (d, 2C), 174.6 (s); IR (thin film) 2940, 1735, 1640, 1440, 1230, 920, 755 cm^{-1}; EIMS *m /z* 323 (M^+), 282, 264, 227, 195; HRFABMS Calcd. for $C_{21}H_{26}N_1O_2$: 324.1964; Found: 324.1992.

δ-Amino acid methyl ester 9g. A solution of **8g** (362 mg, 1.0 mmol) and Wilkinson catalyst (53 mg, 0.057 mmol) in MeCN-H_2O (84 : 16, 25 ml) was refluxed for 90 minutes according to Ganem's procedure.[17] The resulting mixture was concentrated and purified directly by silica gel column chromatography (20 % ethanol / ethyl acetate) to give d-amino acid methyl ester **9g** (223 mg, 79 %) as a clear oil; ^{1}H NMR (270 MHz, $CDCl_3$) 1.73 (s, 2H, $N\underline{H_2}$), 2.78 (bdd, J = 14.2, 6.9, 1H), 2.87 (bdd, J = 14.2, 7.3, 1H), 3.60 (s, 3H), 4.29 (d, J = 3.6, 1H), 4.86 (bd, J = 9.9, 1H), 4.92 (bd, J = 17.2, 1H), 5.34 (ddt, J = 17.2, 9.9, 6.9, 1H), 5.76 (dd, J = 10.2, 1.3, 1H), 6.16 (dd, J = 10.2, 4.0, 1H), 7.17 ~ 7.35 (m, 3H), 7.45 (dd, J = 7.3, 1.7, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 43.4 (t), 47.9 (d), 50.5 (s), 52.6 (q), 118.3 (t), 126.3 (d), 127.1 (d), 127.5 (d), 127.9 (d), 128.2 (d), 131.2 (d), 133.0 (d), 134.5 (s), 139.5 (s), 174.2 (s); IR (thin film) 3370, 3280, 2950, 1738, 1640, 1495, 1225, 1020, 755 cm^{-1}; EIMS *m /z* 243 (M^+), 228, 210, 201, 170; HRFABMS Calcd. for $C_{15}H_{18}N_1O_2$: 244.1338; Found: 244.1342.

4-Oxa-1,2,3,4-tetrahydronaphthyloxazoline 10 To a stirred, cooled (-78°C) solution of ethyl vinyl ether (65 mg, 0.90 mmol) in tetrahydropyran (0.4 ml) was added *t*-butyllithium (1.60 M of pentane solution, 0.48 ml, 0.77 mmol). The mixture was warmed to -3~-5°C, stirred for 30 minutes, re-cooled to -78°C, diluted with THF (1.0 ml), treated with HMPA (139 mg, 0.77 mmol), stirred for 5 minutes to dissolve HMPA and treated with amino adduct **2f** (100 mg, 0.30 mmol) in THF (0.4 ml). After stirring for 3 hours at -78°C, the mixture was treated with *t*-butanol (0.5 ml), stirred for 10 minutes at -78°C and poured into water, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (50% ethyl acetate / hexane) gave **10** (67 mg, 88 %) as a clear oil; ^{1}H NMR (270 MHz, $CDCl_3$) 1.28 (s, 3H), 1.32 (s, 3H), 1.69 (s, 3H), 2.09 (m, 1H), 2.58 ~ 2.97 (m, 3H), 3.89 (s, 2H), 7.37 (m, 2H), 7.55 (tt, J = 6.9, 1.3, 1H), 8.05 (bd, J = 7.6, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 26.4 (q), 28.2 (q), 28.3 (q), 33.6 (t), 34.8 (t), 40.0 (s), 67.1 (s), 79.2 (t), 127.1 (d), 127.296 (d), 127.33 (d), 131.5 (s), 133.7 (d), 146.3 (s), 168.7 (s), 197.4 (s); IR (thin film) 2950, 1690, 1655, 1600, 1455, 1390, 1195, 770, 710 cm^{-1}; HRFABMS Calcd. for $C_{16}H_{20}N_1O_2$: 258.1494; Found: 258.1477.

2-Methyl-4-oxa-1,2,3,4-tetrahydronaphthyloxazoline 11 This was prepared from amino adduct **2f** by the procedure for **10**. Methyl iodide (119 mg, 0.84 mmol) was used as an electrophile. **11** (66 mg, 82 %) was obtained as a white solid (mixture of β-methyl isomer and α-methyl isomer. The ratio was 95 : 5); ^{1}H NMR (270 MHz, $CDCl_3$) 1.15 (d, J = 6.6, 3H), 1.24 (s, 3H), 1.31 (s, 3H), 1.72 (s, 3H), 2.33 (m, 1H), 2.59 (dd, J = 16.5, 4.3, 1H), 3.02 (dd, J = 16.8, 13.2, 1H), 3.76 (d, J = 8.3, 1H), 3.87 (d, J = 7.9, 1H), 7.36 (bd, J = 7.9, 1H), 7.46 (dd, J = 7.9, 0.7, 1H), 7.55 (td, J = 7.9, 1.7, 1H), 8.05 (dt, J = 7.9, 0.7, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 16.9 (q), 26.0 (q), 28.1 (q), 28.5 (q), 38.0 (d), 43.4 (t), 66.8 (s), 79.0 (t), 127.0 (d), 127.1 (d), 127.2 (d), 132.0 (s), 133.8 (d), 146.3 (s), 167.5 (s), 198.2 (s); IR (thin film) 2950, 1695, 1650, 1595, 1460, 1300, 1100, 780 cm^{-1}; HRFABMS Calcd. for $C_{17}H_{22}N_1O_2$: 272.1651; Found: 272.1645.

2-Ethoxycarbonyl-4-oxa-1,2,3,4-tetrahydronaphthyloxazoline 12 This was prepared from amino adduct **2f** by the procedure for **10**. Ethyl chlorocarbonate (91 mg,

0.84 mmol) was used as an electrophile. **12** (81 mg, 83 %) as a white solid (mixture of β-ethoxycarbonyl isomer and α-ethoxycarbonyl isomer. The ratio was 85 : 15); ^{1}H NMR (270 MHz, $CDCl_3$) 1.22 (s, 3H), 1.27 (t, J = 7.3, 3H), 1.31 (s, 3H), 1.83 (s, 3H), 2.83 (dd, J = 16.8, 4.3, 1H), 3.20 (dd, J = 11.9, 4.3, 1H), 3.42 (dd, J = 16.8, 11.9, 1H), 3.81 (d, J = 7.9, 1H), 3.89 (d, J = 7.9, 1H), 4.17 (m, 2H), 7.32 ~ 7.44 (m, 2H), 7.57 (m, 1H), 8.07 (dd, J = 7.9, 1.6, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 14.1 (q), 26.7 (q), 27.8 (q), 28.0 (q), 37.9 (d), 41.6 (s), 49.4 (d), 61.1 (t), 66.7 (s), 79.3 (t), 126.7 (d), 127.0 (d), 127.5 (d), 131.4 (s), 134.0 (d), 144.5 (s), 166.9 (s), 171.5 (s), 195.7 (s); IR (thin film) 2950, 1740, 1685, 1655, 1595, 1455, 1300, 770 cm^{-1}; HRFABMS Calcd. for $C_{19}H_{24}N_1O_4$: 330.1706; Found: 330.1699.

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