JOC Articles

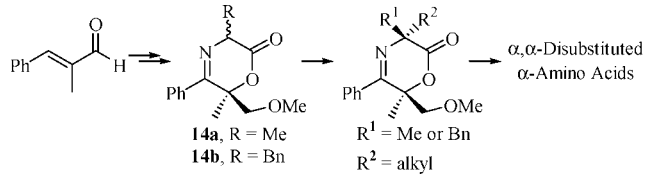
Asymmetric Synthesis of α-Amino Acids: Preparation and Alkylation of Monocyclic Iminolactones Derived from α-Methyl *trans*-Cinnamaldehyde†

Ta-Jung Lu* and Cheng-Kun Lin

Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 40227, Republic of China

tjlu@dragon.nchu.edu.tw

Received July 10, 2008



Two novel chiral monocyclic iminolactones **14a** and **14b** have been prepared. The chiral auxiliary **12** was obtained from α-methyl-*trans*-cinnamaldehyde through reduction, methylation, Sharpless asymmetric dihydroxylation, and oxidation in 87% overall yield. Esterification of compound **12** with the respective protected amino acids followed by deprotection and cyclization provided the corresponding iminolactones, each in 82% overall yield. Alkylation of the iminolactone **14a** afforded the α-methyl-α,α-disubstituted products **15** and **16** in good yields (78−99%) and excellent diastereoselectivity (de >98%). Alkylations of the iminolactone **14b** furnished the α-benzyl-α,α-disubstituted products **15a**, **16b**, **17**, and **18** in good yields (51−86%) but moderate diastereoselectivities (43−56%). When HMPA or DMPU was used as a cosolvent, the rate of alkylation of the iminolactone **14b** was accelerated with improved yields (56−99%) and diastereoselectivities (50−83%). Hydrolysis of the dialkylated iminolactones yielded the α,α-disubstituted α-amino acids in good yields (80−98%) and high enantiomeric excesses (98−99%) with good recovery of compound **12** (83−92%).

Introduction

Asymmetric synthesis of optically active α-amino acids and their derivatives is an important area of great interest for their extensive use in pharmaceuticals,[1] agrochemicals,[2] and as chiral ligands,[3] which has led to the development of many highly enantioselective methodologies.[4] Among those methods, chiral glycine- and alanine-equivalents play an important role.[5] For example, Nájera and co-workers reported a versatile oxazinone system which was used as chiral cyclic alanine-equivalent for the asymmetric synthesis of interesting enantiomerically enriched acyclic and cyclic α-methyl α-amino acids (AMAAs).[5f] Recently, we reported two tricyclic iminolactones **1** and **2** (Scheme 1), prepared from (1*R*)-(+)-camphor, to provide α-monosubstituted α-amino acids in high yields with excellent enantiomeric excesses.[6]

We envisioned a new stereoselective strategy for constructing α-amino acids, as outlined in Scheme 2. Iminolactone **4** should give an enolate when treated with a strong base. The oxygen atom on the sidearm can chelate to the metal cation M^+ to form

† This paper is dedicated to the memory of Professor A. I. Meyers.

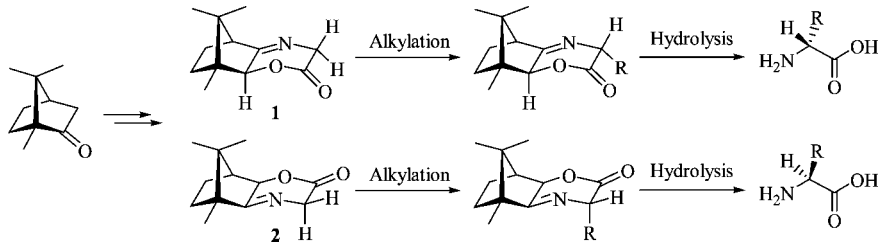
(1) (a) Lee, K.-A.; Yeo, S.; Kim, K. H.; Lee, W.; Kang, S. J. *J. Pharm. Biomed. Anal.* **2008**, *46*, 914–918. (b) Gioia, M. G.; Andreatta, P.; Boschetti, S.; Gatti, R. *J. Pharm. Biomed. Anal.* **2007**, *45*, 456–464. (c) Hicks, R. P.; Bhonsle, J. B.; Venugopal, O.; Koser, B. W.; Magill, A. J. *J. Med. Chem.* **2007**, *50*, 3026–3036. (d) Davtyan, T. K.; Hakobyan, I. S.; Muradyan, R. E.; Hovhannisyan, H. G.; Gabrielyan, E. S. *J. Antimicrob. Chemother.* **2007**, *59*, 1114–1122. (e) Gajewski, M.; Seaver, B.; Esslinger, C. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4163–4166.

(2) (a) Maier, T. H. P. *Nat. Biotechnol.* **2003**, *21*, 422–427. (b) Wakayama, M.; Yoshimune, K.; Hirose, Y.; Moriguchi, M. *J. Mol. Catal. B: Enzym.* **2003**, *23*, 71–85. (c) Claus, M. T.; Zocher, G. E.; Marier, T. H. P.; Schulz, G. E. *Biochemistry* **2005**, *44*, 8620–8626.

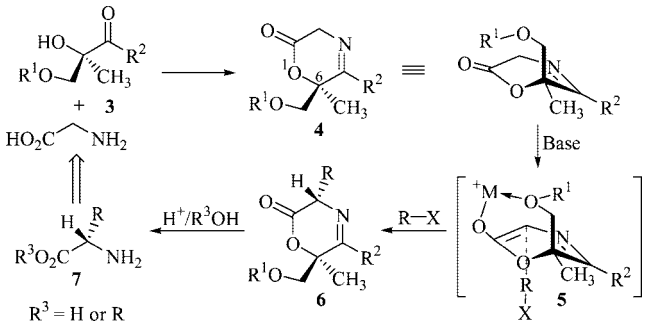
(3) (a) Almansa, R.; Guijamo, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1376–1380. (b) Wettergren, J.; Zaitsev, A. B.; Adolffson, H. *Adv. Synth. Catal.* **2007**, *349*, 2556–2562. (c) Han, Z.-J.; Wang, R.; Zhou, Y.-F.; Liu, L. *Eur. J. Org. Chem.* **2005**, 934–938. (d) Richmond, M. L.; Sprout, C. M.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 8835–8840. (e) Malkov, A. V.; Bourhani, Z.; Koèovský, P. *Org. Biomol. Chem.* **2005**, *3*, 3194–3200. (f) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.

10.1021/jo801514g CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/11/2008

SCHEME 1



SCHEME 2



a rigid complex transition state **5**. Thus, the sidearm would act as an effective blocking group to shield the top face of the enolate and the electrophile should come in from the bottom face. The difference of free energy of activation ($\Delta\Delta G^{\ddagger}$) between the two faces is anticipated to be large. As a result, the diastereomeric excess (de) of the alkylated product should be very high. Compound **6** can then be hydrolyzed to provide the α-monosubstituted α-amino acid or the corresponding amino ester along with the recovered chiral auxiliary **3**.

The cyclic iminolactone **4** was chosen for the following reasons: (a) a cyclic system will allow for a more rigid transition state than the corresponding acyclic one, which can enhance the steric effect of the auxiliary in controlling the stereochemistry of the reaction; (b) unlike acyclic esters, lactones give rise to only the *Z*-enolate, which in turn will afford a single alkylated product if electrophiles approaches specifically from one of the enolate faces; (c) the C(6)-sidearm of the oxazinone ring can block the top face of the alkylation reaction and thus result in good stereoselectivity; and (d) both the imine and lactone functioalities can be hydrolyzed easily to produce the amino acids with possible recovery of the chiral auxiliary.

Herein, we report the development of an alanine equivalent and a phenylalanine equivalent of monocyclic iminolactones and their application for the asymmetric syntheses of α-methyl and α-benzyl-α,α-disubstituted α-amino acids.

Results and Discussion

The first task of our synthesis was the preparation of the chiral auxiliary in high optical purity. Based on our retrosynthetic analysis, the chiral auxiliary hydroxyketone **12** could be prepared from α-methyl-*trans*-cinnamaldehyde. First, reduction of the aldehyde **8** with sodium borohydride produced the allylic alcohol **9**. In this transformation, we found that the addition of a solution of aldehyde **8** in 95% ethanol dropwise into sodium borohydride without cerium trichloride[7] could give the reduced product in 99% yield. The primary alcohol was then converted smoothly into its corresponding methyl ether **10**.[8] The stereocenters of the chiral auxiliary were established by Sharpless asymmetric dihydroxylation to yield the diol **11** in 93% yield and 98% e.e.[9] The diol **11** was subsequently oxidized with IBX (2-iodoxybenzoic acid) in acetonitrile containing two equivalents of water to obtain hydroxyketone **12** in 75% (93% based on recovered starting material) yield (Scheme 3).[10]

Chiral auxiliary **12** was then coupled with Boc-*dl*-alanine or Boc-*dl*-phenylalanine, mediated by DCC (*N*,*N*′-dicyclohexylcarbodiimide) and DMAP [4-(dimethylamino)pyridine],[11] to furnish the ester **13** (Scheme 4). After flash column purification of the crude ester, removal of the Boc group was achieved by bubbling with gaseous HCl to afford the amine hydrogen chloride salt. Treatment of this salt with anhydrous potassium carbonate in acetonitrile gave two inseparable diastereomers of the desired iminolactone **14** in 82% yields over three steps.

The iminolactone **14a** was deprotonated with LDA at −78 °C and alkylated with benzyl bromide to give the diastereomer **15a** in 83% yield and excellent de (98%) (Scheme 5).

As summarized in Table 1, alkylation reactions of the iminolactone **14** generated the dialkylated products in good yields with extremely high control of the stereochemistry of the α-carbon for a number of electrophiles.

When *n*-propyl iodide and isobutyl bromide were used as electrophiles (Table 1, entries 5 and 6), the iminolactone **14a**

(4) (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889–917. (c) Xu, P.-F.; Li, S.; Lu, T.-J.; Wu, C.-C.; Fan, B.-T.; Golfis, G. *J. Org. Chem.* **2006**, *71*, 4364–4373. (d) Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215. (e) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. (f) Wanner, K.; Koch, C. J.; Šimonyiová, S.; Pabel, J.; Kärtner, A.; Polborn, K. *Eur. J. Org. Chem.* **2003**, 1244–1263. (g) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (h) Schöllkopf, U.; Kühnle, W.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 480–482. (i) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (j) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, 1337. (k) Carloni, A.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1998**, *9*, 2987–2998. (l) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (m) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. (n) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–632.

(5) For glycine equivalents, see: (a) Saghiyan, A. S.; Dadayan, S. A.; Petrosyan, S. G.; Manasyan, L. L.; Geolchanyan, A. V.; Djamgaryan, S. M.; Andreasyan, S. A.; Maleev, V. I.; Khrustalev, V. N. *Tetrahedron: Asymmetry* **2006**, *17*, 455–467. (b) Kitamura, M.; Arimura, Y.; Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2008**, *49*, 2026–2030. (c) Ma, D.; Ding, K. *Tetrahedron* **2001**, *57*, 6361–6366. (d) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3–15. (e) Chinchilla, R.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2006**, *17*, 3423–3429. (f) For alanine equivalents, see: Nájera, C.; Chinchilla, R.; Galindo, N. *Synthesis* **1999**, 704–717. (g) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233–1238. (h) Nájera, C.; Abellán, T.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2809–2820. (i) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245–7248.

(6) (a) Xe, P.-F.; Chen, Y.-S.; Lin, S.-I.; Lu, T.-J *J. Org. Chem.* **2002**, *67*, 2309–2314. (b) Xe, P.-F.; Lu, T.-J. *J. Org. Chem.* **2003**, *68*, 658–661.

(7) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

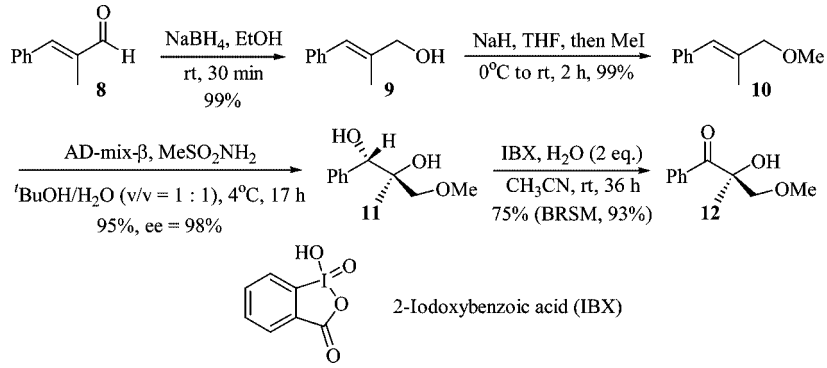
(8) Uang, B.-J.; Chen, T.-Y.; Yeu, J.-P.; Yeh, J.-T. *Synthesis* **2001**, 1775–1777.

(9) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Grispino, G. A.; Hartung, J. H.; Jeong, K.-S. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Gonzalez, J.; Aurigemma, C.; Truesdale, L. *Org. Synth.* , *79*, 93–103.

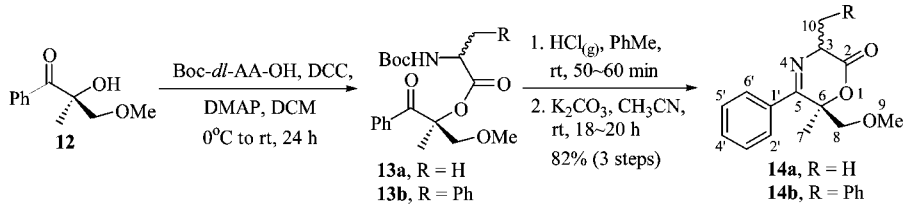
(10) (a) Martin, J. C.; Dess, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1999**, *58*, 2899.

(11) Gu, D.-X. Master Thesis, National Chung-Hsing University, 2003.

SCHEME 3



SCHEME 4



SCHEME 5

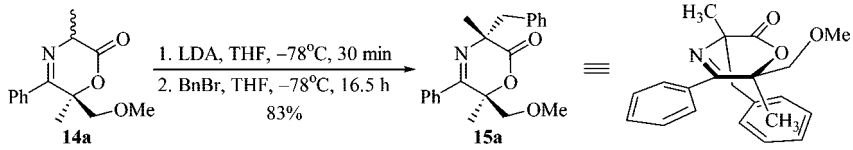
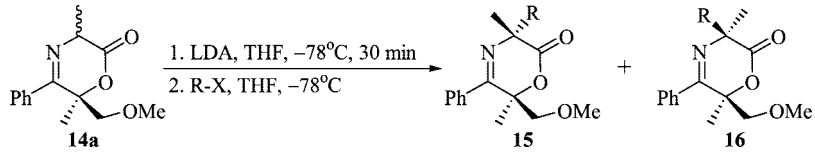


TABLE 1. Alkylation of the Iminolactone 14a



entry	RX	R	time (h)	yield[a] (%)	de[b] (%)
1	$PhCH_2Br$	$PhCH_2$	16.5	83 (**15a**)	>98
2	EtO_2CCH_2Br	EtO_2CCH_2	15.5	99 (**15b**)	>98
3	$NCCH_2Br$	$NCCH_2$	15.5	91 (**15c**)	>98
4	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2$	18.5	78 (**15d/16d**)	69
5	$CH_3(CH_2)_2I$	$CH_3(CH_2)_2$	15.5	*c*	
6	$(CH_3)_2CHCH_2Br$	$(CH_3)_2CHCH_2$	15.5	*c*	

[a] The reported yields are isolated yields after column chromatography. [b] Diastereomeric excess was estimated by ^1H NMR integrations of the crude reaction mixtures on a 400 NMR spectrometer. [c] No reaction.

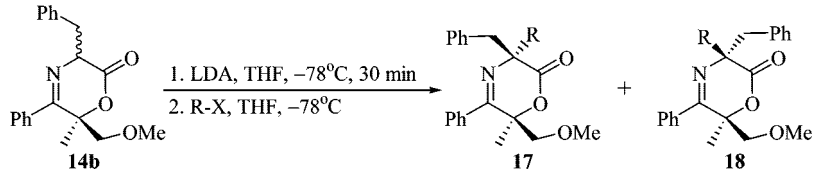
failed to give desired products which might because of the rate of the competitive elimination is faster than that of the alkylation. It is noteworthy that allylation of the oxazinone **14a** with allyl bromide resulted in an unexpectedly poor diastereoselectivity compared with other active alkyl halides (Table 1, entry 4).

Table 2 describes the yields and de of the alkylated products of the iminolactone **14b** under different alkylation conditions. Alkylations were carried out at −78 °C using LDA as the base to give the dialkylated products in moderate to good yields but in unsatisfactory stereoselectivities (Table 2, entries 1, 7, and 10). The reaction rates were effectively accelerated by the addition of HMPA (hexamethylphosphoramide) or DMPU (*N,N′*-dimethylpropylene urea), and the diastereoselectivities were significantly enhanced as a result (Table 2, entries 2, 5, 6, 8, 9, 11, and 12). The considerable improvement of the facial selectivities presumably was due to a decrease in the degree of aggregation of the enolate.[12] The use of chelating agents such as $ZnBr_2$ and ZnI_2, in a hope to increase the chelation of the metal ion and the oxygen atom on the sidearm to improve the facial selectivity, did not deliver satisfactory results (Table 2, entries 13 and 14).

The stereochemistry of the newly created stereocenter of the dialkylated product is deduced from the following evidence: The ^1H NMR spectra of the dialkylated derivatives **15a**, **16a**, **17**, and **18** with a C(3)-benzyl group showed a remarkable stereochemistry-dependent shielding effect on the chemical shifts of the methyl group and the methoxy group on C(6). The chemical shifts of characteristic protons of compounds **15a**, **16a**,

(12) Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343–5346.

TABLE 2. Alkylation of the Iminolactone 14b

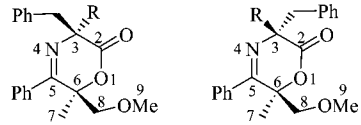


14b **17** **18**

	reaction conditions			
entry	deprotonation	alkylation	yield[a] (%)	de[b] (%)
1	LDA, THF, −78 °C, 0.5 h	CH_3I, −78 °C, 15.5 h	75 (**16a/15a**)	43
2	LDA, THF/HMPA, −78 °C, 1 h	CH_3I, −78 °C, 1 h	87 (**16a/15a**)	50
3	LDA, THF/DMPU, −78 °C, 1 h	CH_3I, −78 °C, 1 h	84 (**16a/15a**)	15
4	LDA, THF, −78 °C, 0.5 h	CH_3CH_2I, −78 °C, 16.5 h	*c*	
5	LDA, THF/HMPA, −78 °C, 1 h	CH_3CH_2I, −78 °C, 1 h	95 (**17a/18a**)	75
6	LDA, THF/DMPU, −78 °C, 1 h	CH_3CH_2I, −78 °C, 1 h	56 (**17a/18a**)	55
7	LDA, THF, −78 °C, 0.5 h	$NCCH_2Br$, −78 °C, 20 h	86 (**17b/18b**)	53
8	LDA, THF/HMPA, −78 °C, 1 h	$NCCH_2Br$, −78 °C, 1 h	96 (**17b/18b**)	83
9	LDA, THF/DMPU, −78 °C, 1 h	$NCCH_2Br$, −78 °C, 1 h	99 (**17b/18b**)	82
10	LDA, THF, −78 °C, 0.5 h	CH_2=$CHCH_2Br$, −78 °C, 13.5 h	51 (**17c/18c**)	56
11	LDA, THF/HMPA, −78 °C, 1 h	CH_2=$CHCH_2Br$, −78 °C, 1 h	83 (**17c/18c**)	76
12	LDA, THF/DMPU, −78 °C, 1 h	CH_2=$CHCH_2Br$, −78 °C, 1 h	93 (**17c/18c**)	70
13	LDA, THF, $ZnBr_2$, −78 °C, 1 h	CH_2=$CHCH_2Br$, −78 °C, 12 h	38 (**17c/18c**)	64.5
14	LDA, THF, ZnI_2, −78 °C, 1 h	CH_2=$CHCH_2Br$, −78 °C, 12 h	68 (**17c/18c**)	65

[a] The reported yields are isolated yields after column chromatography. [b] Diastereomeric excess was estimated by ^{1}H NMR integrations of the crude reaction mixtures on a Varian Mercury-400 NMR spectrometer. [c] No reaction.

TABLE 3. Chemical Shifts of Characteristic Protons of Compounds 15a, 16a, 17, and 18



16a, 17 **15a, 18**

compd	R	α_{C7-CH3}	α_{C8-CH2}	α_{C9-CH3}
16a	CH_3	1.47	3.51, 3.15	2.92
15a	CH_3	0.54	3.45, 3.09	3.35
17a	CH_3CH_2	1.43	3.47, 3.16	2.96
18a	CH_3CH_2	0.33	3.42, 3.09	3.28
17b	$NCCH_2$	1.55	3.43, 3.21	3.10
18b	$NCCH_2$	0.53	3.42, 3.26	3.32
17c	CH_2=$CHCH_2$	1.40	3.51, 3.20	2.91
18c	CH_2=$CHCH_2$	0.39	3.44, 3.15	3.28

17, and **18** are compiled in Table 3. For instance, before alkylation, the chemical shifts of the C(6)-methyl groups of the two diastereomers of iminolactone **14a** are δ 1.40 and 1.46 ppm, respectively. After benzylation, the C(6)-methyl group of the product **15a** moved to δ 0.54. The methyl group of the MOM group at C(6) of compound **16a** (δ 2.92) appeared at 0.43 ppm higher field than that of compound **15a** (δ 3.35). The shielding effect of the C(3)-benzyl group is responsible for this upfield shift, indicating that the C(3)-benzyl group and C(6)-methyl group must lie in the same side of the oxazinone ring while the C(6)-MOM group of compound **16a** and the C(3)-benzyl group are on the same side of the oxazinone ring.

On the other hand, the chemical shifts of the methylene of the C(6)-MOM groups were nearly unaffected by the relative position of the C(3)-benzyl group (0.01−0.07 ppm). The small chemical shift differences of the methylene of C(6)-MOM groups between the major and minor products (0.22−0.43 ppm) suggested that the steric interaction between the C(6)-MOM groups and the C(3)-benzyl groups of the major products pushed the phenyl ring away from the C(6)-MOM groups.

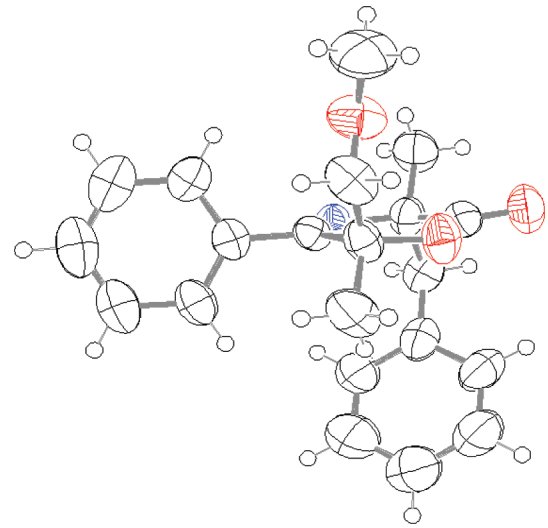


FIGURE 1. X-ray structure of compound **15a**.

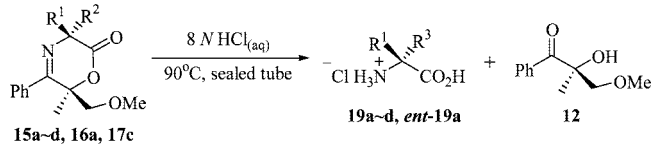
The stereochemistry of the alkylated product serves to demonstrate that benzyl bromide reacted with the enolate from the opposite side of the sidearm in the alkylation step as predicted by our transition-state model.

Furthermore, X-ray determination of a single crystal of **15a**,[13] recrystallized from ether/hexane, clearly shows that the C(6)-methyl group sits right on top of the benzene ring of the C(3)-benzyl group which is strongly shielded by its ring current (Figure 1). This result confirms the stereochemistry assignment by ^{1}H NMR data.

To obtain α-amino acids, the disubsituted iminolactones were heated with 8 N HCl aqueous solution in a sealed tube at 90 °C (Table 4). After hydrolysis, the corresponding α,α-dialkylated α-amino acid hydrogen chloride salts were obtained in high

(13) The X-ray crystallographic structure of compound **15a** has been submitted to the Cambridge Crystallographic Data Centre. The CCDC number for compound **15a** is CCDC 669087.

TABLE 4. Hydrolysis of the Dialkylated Iminolactones 15a−d, 16a, and 17c



15a~d, 16a, 17c **19a~d, *ent*-19a** **12**

substrate	R^1	R^2	R^3	amino acid (%)	recovered chiral auxiliary (%)	time (h)	$[\alpha]^{23}_D$	ee[d] (%)
15a	CH_3	$PhCH_2$	$PhCH_2$	92 (**19a**)	83	1	+9.40[a]	98
15b	CH_3	EtO_2CCH_2	HO_2CCH_2	98 (**19b**)	92	3	−36.2[b]	99
15c	CH_3	$NCCH_2$	HO_2CCH_2	94 (**19b**)	90	3	−35.5[b]	99
15d	CH_3	CH_2=$CHCH_2$	CH_2=$CHCH_2$	85 (**19c**)	89	3	+13.4[c]	98
16a	$PhCH_2$	CH_3	CH_3	91 (*ent*-**19a**)	85	1	−9.41[a]	99
17c	$PhCH_2$	CH_2=$CHCH_2$	CH_2=$CHCH_2$	80 (**19d**)	87	3	+15.3[a]	98

[a] The optical rotations were measured in H_2O solution. [b] The optical rotations were measured in MeOH solution. [c] The optical rotations was measured in D_2O solution. [d] e.e.% values were determined by chiral HPLC analyses.

yields and excellent ee. The configuration of the resulting amino acids was determined by comparing the optical rotations of the products with literature values. Additionally, the chiral auxiliary **12** was recovered in excellent yields (83−92%).

Conclusion

In conclusion, an efficient method for preparation of chiral auxiliary **12** was developed which was utilized in the construction of two novel chiral iminolactone templates **14a** and **14b**. The alkylation of them gave the dialkylated products in high yields and facial selectivities in a stereochemistry predictable by our transition state model. Hydrolysis of the iminolactones afforded the desired α,α-disubstituted α-amino acids in excellent yields and optical purity. The ease of syntheses of and the good yields and the high stereoselectivities realized in the alkylation of the iminolactone templates as well as the possibility of recycling of the chiral auxiliaries rendered our method a practical and useful protocol for preparation of enantiopure α-amino acids in predetermined stereochemistry. If $(DHQ)_2$-PHAL [1,4-bis(9-O-dihydroquinine)phthalazine) was used in the asymmetric dihydroxylation reaction, the antipode of chiral auxiliary **12** can be obtained. Consequently, either enantiomer of an α-amino acid can be synthesized selectively. The application of our methodology in the synthesis of biologically active α,α-disubstituted amino acids is in progress.

Experimental Section

General Methods. All alkylation reactions were conducted in flame-dried Schlenk tubes fitted with rubber septa under an argon atmosphere, and all reactions were carried out under a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Chloroform (δ = 7.26) or deuterium oxide (δ = 4.60) was used as internal standard in ^{1}H NMR spectra. The center peak of deuterochloroform (δ = 77.0) was used as internal standard in ^{13}C NMR spectra. The ee value of the α-amino acids obtained from hydrolysis of the alkylated iminolactones was determined by HPLC analysis on a Crownpak CR(+) column (Daicel column, 150 mm × 4 mm) using water and ethanol as the mobile phase.

Materials. Reagents and solvents are commercially available. All alkyl halides were pretreated with copper powder. Diisopropylamine, toluene, dichloromethane (DCM), acetonitrile, HMPA, and DMPU were distilled from calcium hydride immediately prior to use, THF was distilled from sodium benzophenone ketyl, and *n*-butylithium in hexanes (nominally 1.6 M) was purchased from Aldrich. IBX,[10] Boc-*dl*-alanine, and Boc-*dl*-phenylalanine[14] were prepared according to the literature procedures.

(*E*)-2-Methyl-3-phenylprop-2-en-1-ol (9).[15] A solution of α-methyl *trans*-cinnamaldehyde (6.66 g, 44.7 mmol) in 95% EtOH (90 mL) was added to $NaBH_4$ (2.18 g, 1.2 equiv) in an ice−water bath over a 20 min period. Saturated NH_4Cl aqueous solution (25 mL) and water (25 mL) were added to the reaction mixture, which was kept stirring for 60 min. The mixture was extracted with ether. The combined organic phases were washed with brine, dried (anhyd $MgSO_4$), and concentrated to give a colorless oily product (6.55 g, 99%). This crude allylic alcohol was pure enough for further use. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.35 (m, 5H, Ph), 6.53 (s, 1H, CH), 4.18 (s, 2H, CH_2), 1.90 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 128.7, 127.9, 126.2, 124.6, 68.4, 15.1. MS: *m*/*z* 148 (M^+, 23.0), 131 (100), 115 (55.9), 91 (83.6). HRMS *m*/*z* calcd for $C_{10}H_{12}O$ M^+ 148.0888, found M^+ 148.0881.

[(*E*)-3-Methoxy-2-methylpropenyl]benzene (10). A solution of (*E*)-2-methyl-3-phenylprop-2-en-1-ol (**9**) (2.23 g, 15.0 mmol) in dry THF (15 mL) was dropped to a stirred suspension of 95% sodium hydride (645 mg, 1.7 equiv) in dry THF (35 mL) in an ice−water bath under nitrogen over 15 min period, and then iodomethane (1.4 mL, 1.5 equiv) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h before 4 N NaOH aqueous solution (19 mL) was added. The mixture was vigorously stirred overnight. The aqueous layer was extracted with ether. The combined organic extracts were dried (anhyd $MgSO_4$) and concentrated to give crude orange liquid. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:1) to give methyl ether (2.41 g, 99%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.35 (m, 5H, Ph), 6.50 (s, 1H, CH), 3.98 (s, 2H, CH_2), 3.37 (s, 3H, OCH_3), 1.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 134.9, 128.8, 128.0, 126.8, 126.3, 78.6, 57.6, 15.2. MS: *m*/*z* 162 (M^+, 27.3), 145 (70.8), 115 (100), 105 (86.4), 91 (86.2), 77 (60.7), 51 (30.9). HRMS *m*/*z* calcd for $C_{11}H_{14}O$ M^+ 162.1045, found M^+ 162.1043.

(1*S*,2*S*)-3-Methoxy-2-methyl-1-phenylpropane-1,2-diol (11). A 1000 mL flask with a mechanical stirrer was charged with *tert*-buyl alcohol (130 mL), water (130 mL), potassium osmate dihydrate (29 mg, 0.3 mol%), $(DHQD)_2$-PHAL [1,4-bis(9-*O*-dihydroquinidine)phthalazine, 215 mg, 1.0 mol%], potassium ferricyanide (26.0 g, 3.0 equiv), potassium carbonate (10.8 g, 3.0 equiv), and methanesulfonamide (2.53 g, 1.0 equiv). Stirring at room temperature produced two clear phases; the lower aqueous phase appears bright yellow. The mixture was cooled to 4 °C whereupon some of the dissolved salts precipitated. Methyl ether **10** (4.22 g, 26.0

(14) Adolfsson, H.; Pastor, I. M.; Västilä, P. *Chem.—Eur. J.* **2003**, *9*, 4031–4045.

(15) (a) Goodwin, T. E.; Ratcliff, D. G.; Crowder, C. M.; Seitzinger, N. K. *J. Org. Chem.* **1982**, *47*, 815–820. (b) Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A *J. Org. Chem.* **1997**, *62*, 1976–1985.

mmol) was added at once, and the heterogeneous slurry was stirred vigorously at 4 °C for 17 h. While the mixture was stirred in an ice−water bath, solid sodium sulfite (39.7 g) was added and stirred for 1 h. EtOAc was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with EtOAc. The organic phases were washed with 2 N KOH aqueous solution (2 × 10 mL) with vigorous shaking to remove methanesulfonamide. The organic extract was dried (anhyd $MgSO_4$) and concentrated to give the diol and the ligand. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 5: 1, then 2: 1) to give the desired diol (4.87 g, 95%) as a colorless viscous oil. $[\alpha]^{23}_D = -20.2$ ($c = 1.70$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3439 (br), 3031 (m), 2981 (s), 2931 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.40 (m, 5H, Ph), 4.79 (s, 1H, CH), 3.44 (s, 3H, OCH_3), 3.40 (d, $J = 9.2$ Hz, 1H, CH_2), 3.30 (d, $J = 9.2$ Hz, 1H, CH_2), 0.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 127.8, 127.5, 127.4, 78.3, 77.1, 74.3, 59.1, 18.9. MS: *m/z* 196 (M^+, 0.2), 133 (19.9), 111 (83.8), 89 (100), 79 (63.0), 57 (46.4). HRMS *m/z* calcd for $C_{11}H_{16}O_3$ M^+ 196.1129, found M^+ 196.1106. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 65.02; H, 7.66.

(*S*)-2-Hydroxy-3-methoxy-2-methyl-1-phenylpropan-1-one (12).[16] IBX (6.06 g, 1.8 equiv) was added to a solution of the diol **11** (2.33 g, 11.9 mmol) in MeCN (27 mL) and water (390 μL, 2 equiv). After being stirred at room temperature for 36 h, the reaction mixture was filtered by a pad of Celite and concentrated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 5:1 then 2: 1) to give hydroxyketone **12** (1.73 g, 75%) as a colorless liquid and the recovered starting material (443 mg, 19%). $[\alpha]^{23}_D = -47.0$ ($c = 1.50$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3449 (br), 2984 (s), 2932 (s), 1677 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01−8.03 (m, 2H, Ph), 7.43−7.56 (m, 3H, Ph), 3.99 (d, $J = 9.2$ Hz, 1H, CH_2), 3.49 (d, $J = 9.6$ Hz, 1H, CH_2), 3.35 (s, 3H, OCH_3), 1.51 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 135.2, 132.4, 129.2, 128.1, 79.6, 78.5, 59.3, 23.3. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.68; H, 6.90.

(3*RS*,6*R*)-6-(Methoxymethyl)-6-methyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (14a). To a solution of the hydroxyketone **12** (1.74 g, 8.95 mmol), DMAP (1.11 g, 1.0 equiv), and Boc-*dl*-alanine (3.39 g, 2.0 equiv) in DCM (10 mL) in an ice−water bath was added DCC (3.72 g, 2.0 equiv) in DCM (8 mL), and the reaction mixture was stirred at 0 °C (ice−water bath). The mixture was allowed to warm to room temperature and kept stirring for 24 h. Ether was added to the mixture, the precipitate was filtered through a pad of Celite, washed several times with EtOAc, and the solvent was concentrated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 5:1) to give **13a** as a colorless viscous oil. The ester **13a** (8.95 mmol) was dissolved in toluene (30 mL) and bubbled with gaseous HCl, and the mixture was stirred for 50 min. The solvent and excess gaseous HCl were removed to give ester·hydrochloride as a pale yellow solid. The ester·hydrochloride (8.95 mmol) and K_2CO_3 (3.72 g, 3.0 equiv) were dissolved in acetonitrile (25 mL). The mixture was stirred for 20 h at room temperature, filtered through a pad of Celite, and then concentrated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 5:1) to give the iminolactone **14a** [1:1 (C3-α-methyl/C3-β-methyl, inseparable), 1.81 g, 82% (three steps)] as a colorless oil. IR (NaCl, $CHCl_3$): 3059 (m), 2986 (s), 1747 (s), 1666 (ms) cm^{-1}. MS: *m/z* 247 (M^+, 9.7), 172 (40.8), 131 (100), 104 (41.7), 89 (41.1), 77 (35.1), 56 (66.7). HRMS: *m/z* calcd for $C_{14}H_{17}NO_3$ M^+ 247.1208, found M^+ 247.1209. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.40; N, 5.39.

(3*RS*,6*R*)-3-Benzyl-6-(methoxymethyl)-6-methyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (14b). To a solution of the hydroxyketone **12** (643 mg, 3.31 mmol), DMAP (402 mg, 1.0 equiv), Boc-*dl*-phenylalanine (1.73 g, 2.0 equiv), and in DCM (25 mL) in an ice−water bath was added DCC (1.36 g, 2.0 equiv) in DCM (8 mL), and the reaction mixture was stirred at 0 °C (ice−water bath). The mixture was allowed to warm to room temperature and kept stirring for 24 h. Ether was added to the reaction mixture, which was filtered through a pad of Celite and washed several times with EtOAc, and the solvent was concentrated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 5:1) to give **13b** as a colorless viscous oil. The ester **13b** (3.31 mmol) was dissolved in toluene (22 mL) and bubbled with gaseous HCl, and the mixture was stirred for 1 h. The solvent and excess of gaseous HCl were removed to give ester·hydrochloride as a yellow solid. The ester·hydrochloride (3.31 mmol) and K_2CO_3 (1.38 g, 3.0 equiv) were dissolved in acetonitrile (17 mL). The mixture was stirred for 18 h at room temperature, filtered through a pad of Celite, and then concentrated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 5:1) to give the iminolactone **14b** [4: 1 (C3-α-benzyl/C3-β-benzyl, inseparable), 882 mg, 82% (three steps)] as a white solid. IR (NaCl, $CHCl_3$): 3029 (m), 2990 (s), 2932 (s), 1741 (s), 1666 (ms) cm^{-1}. MS: *m/z* 323 (M^+, 49.3), 278 (99.7), 250 (50.0), 206 (75.5), 131 (64.4), 120 (100), 105 (64.8), 91 (86.6), 77 (29.6), 57 (20.5). HRMS *m/z* calcd for $C_{20}H_{21}NO_3$ M^+ 323.1521, found M^+ 323.1526. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.08; H, 6.26; N, 4.06.

Alkylations of the Iminolactone 14a. Synthesis of Compounds 15 and 16: General Procedure. A solution of LDA (1.3 equiv) [diisopropylamine (180 μL, 1.3 equiv) in dry THF (500 μL) in a flame-dried Schlenk tube under a argon atmosphere was immersed in an ice−water bath, a 1.6 M solution of *n*-butyllithium in hexane (810 μL, 1.3 equiv) was slowly added to the stirred solution, and the mixture was vigorously stirred for 30 min in an ice−water bath] was added dropwise over a period of 10 min to a solution of the iminolactone **14a** (1.00 mmol) in THF (1 mL) at −78 °C. The resulting mixture was stirred at −78 °C for another 20 min. A solution of alkyl halide (3.0 equiv) in dry THF (500 μL) was injected slowly using a syringe pump over 30 min with the needle contacting the wall of the tube allowing the reagent to cool to the reaction temperature before it reached the reaction mixture by dripping along the flask wall. The well-stirred reaction was then kept at −78 °C until completion (progress was monitored by TLC), the solvent was evaporated, and the residue was analyzed by ^1H NMR to determine the diastereomeric excess. Further purification by flash column chromatography (silica gel, hexane/EtOAc = 5:1) afforded the corresponding major diastereomers **15** (Table 1).

(3*R*,6*R*)-3-Benzyl-6-(methoxymethyl)-3,6-dimethyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (15a). Yield: 280 mg (83%). White solid. Mp = 69−73 °C. $[\alpha]^{23}_D = +43.2$ ($c = 0.69$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3064 (m), 2984 (s), 2930 (s), 1733 (s), 1685 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17−7.39 (m, 10H, Ph), 3.45 (d, $J = 12.8$ Hz, 1H, CH_2), 3.37 (d, $J = 10.4$ Hz, 1H, CH_2), 3.35 (s, 3H, OCH_3), 3.15 (d, $J = 10.4$ Hz, 1H, CH_2), 3.09 (d, $J = 12.8$ Hz, 1H, CH_2), 1.75 (s, 3H, CH_3), 0.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 164.8, 138.1, 136.4, 130.6, 128.8, 128.4, 128.0, 127.1, 127.1, 85.5, 76.0, 62.9, 59.1, 47.7, 28.0, 21.0. MS: *m/z* 337 (M^+, 13.7), 293 (72.0), 262 (55.8), 246 (32.9), 202 (100), 131 (84.6), 105 (53.0), 91 (99.2), 77 (26.9), 57 (10.6). HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$ M^+ 337.1678, found M^+ 337.1670. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.39; H, 6.89; N, 4.08.

Ethyl 2-[(3*R*,6*R*)-3,6-Dihydro-6-(methoxymethyl)-3,6-dimethyl-2-oxo-5-phenyl-2*H*-1,4-oxazin-3-yl]acetate (15b). Yield: 330 mg (99%). White solid. Mp = 74−76 °C. $[\alpha]^{23}_D = +3.42$ ($c = 1.2$, $CHCl_3$). IR (NaCl, $CHCl_3$): 2986 (s), 2936 (s), 1734 (s), 1681 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.39 (m, 5H, Ph), 4.12 (dq, $J = 7.2$, 2.4 Hz, 2H, CH_2), 3.69 (d, $J = 10.4$ Hz, 1H, CH_2), 3.46 (d, $J = 10.4$ Hz, 1H, CH_2), 3.42 (s, 3H, OCH_3), 3.32 (d, $J = 17.2$ Hz, 1H, CH_2), 2.85 (d, $J = 17.2$ Hz, 1H, CH_2), 1.59 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.24 (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 170.8, 165.7, 138.1, 129.0,

(16) Liu, X.-L. Master Thesis, National Chung-Hsing University, 1990.

128.5, 127.2, 87.3, 76.3, 60.6, 59.0, 58.2, 45.5, 27.7, 21.9. MS: *m/z* 333 (M^+, 1.9), 289 (15.3), 258 (54.3), 184 (29.6), 142 (38.8), 114 (21.7), 104 (100), 77 (15.7). HRMS: *m/z* calcd for $C_{18}H_{23}NO_5$ M^+ 333.1576, found M^+ 333.1567. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 65.29; H, 6.35; N, 4.37.

2-[(3*R*,6*R*)-3,6-Dihydro-6-(methoxymethyl)-3,6-dimethyl-2-oxo-5-phenyl-2*H*-1,4-oxazin-3-yl]acetonitrile (15c). Yield: 261 mg (91%). White solid. Mp = 149−152 °C. $[\alpha]^{23}_D = -35.7$ ($c = 1.36$, $CHCl_3$). IR (NaCl, $CHCl_3$): 2991 (s), 2244 (m), 1731 (s), 1680 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.45 (m, 5H, Ph), 3.77 (d, $J = 10.4$ Hz, 1H, CH_2), 3.48 (d, $J = 10.8$ Hz, 1H, CH_2), 3.43 (s, 3H, OCH_3), 3.13 (d, $J = 16.0$ Hz, 1H, CH_2), 2.88 (d, $J = 16.0$ Hz, 1H, CH_2), 1.68 (s, 3H, CH_3), 1.48 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 167.7, 137.2, 129.5, 128.7, 127.1, 116.5, 87.8, 76.1, 59.3, 59.1, 31.1, 27.1, 22.9. MS: *m/z* 286 (M^+, 29.1), 246 (25.2), 211 (78.4), 170 (100), 129 (90.0), 115 (35.7), 104 (84.7), 95 (75.2), 89 (46.9), 77 (34.9), 51 (12.4). HRMS: *m/z* calcd for $C_{16}H_{18}N_2O_3$ M^+ 286.1317, found M^+ 286.1311. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.09; H, 6.33; N, 9.33.

(3*R*,6*R*)-3-Allyl-6-(methoxymethyl)-3,6-dimethyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (15d). Yield: 190 mg (66%). White solid. Mp = 56−58 °C. $[\alpha]^{23}_D = -51.0$ ($c = 0.42$, $CHCl_3$). IR (NaCl, $CHCl_3$): 2984 (s), 2937 (s), 1737 (s), 1670 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.41 (m, 5H, Ph), 5.69 (m, 1H, CH), 5.19 (m, 2H, CH_2), 3.66 (d, $J = 10.4$ Hz, 1H, CH_2), 3.41 (s, 3H, OCH_3), 3.39 (d, $J = 10.4$ Hz, 1H, CH_2), 2.84 (dd, $J = 13.2$, 7.2 Hz, 1H, CH_2), 2.60 (dd, $J = 13.2$, 7.2 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 164.9, 138.1, 132.7, 129.0, 128.5, 127.3, 119.5, 86.5, 76.3, 61.5, 59.1, 46.2, 27.4, 22.6. MS: *m/z* 287 (M^+, 39.9), 242 (35.2), 202 (53.3), 171 (39.2), 157 (29.1), 131 (100), 115 (48.9), 104 (62.4), 96 (66.2), 68 (85.1), 53 (31.3). HRMS: *m/z* calcd for $C_{17}H_{21}NO_3$ M^+ 287.1521, found M^+ 287.1521. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.96; H, 7.25; N, 4.66.

(3*S*,6*R*)-3-Allyl-6-(methoxymethyl)-3,6-dimethyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (16d). Yield: 34 mg (12%). Colorless oil. $[\alpha]^{23}_D = -1.66$ ($c = 7.70$, $CHCl_3$). IR (NaCl, $CHCl_3$): 2981 (s), 2932 (s), 1742 (s), 1668 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.42 (m, 5H, Ph), 5.78−5.88 (m, 1H, CH), 5.09−5.18 (m, 2H, CH_2), 3.53 (d, $J = 10.4$ Hz, 1H, CH_2), 3.36 (d, $J = 10.4$ Hz, 1H, CH_2), 3.32 (s, 3H, OCH_3), 2.83 (dd, $J = 14.0$, 7.2 Hz, 1H, CH_2), 2.67 (dd, $J = 14.0$, 7.2 Hz, 1H, CH_2), 1.59 (s, 3H, CH_3), 1.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 166.0, 137.7, 133.1, 129.2, 128.5, 127.5, 118.4, 86.8, 76.2, 60.8, 59.1, 45.4, 27.8, 22.9. MS: *m/z* 287 (M^+, 75.3), 242 (42.7), 212 (100), 202 (77.4), 170 (47.7), 157 (42.6), 131 (99.6), 115 (54.6), 104 (58.8), 96 (53.1), 91 (27.3), 77 (29.4), 68 (49.8), 53 (18.2). HRMS: *m/z* calcd for $C_{17}H_{21}NO_3$ M^+ 287.1521, found M^+ 287.1514. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.92; H, 7.31; N, 4.63.

Alkylations of the Iminolactone 14b. Synthesis of Compounds 15a, 16a, 17, and : General Procedure A (without Additive). A solution of LDA (1.3 equiv) was added dropwise over a period of 10 min to a solution of iminolactone **14b** (0.60 mmol) in THF (2.4 mL) at −78 °C. The resulting mixture was stirred at −78 °C for another 20 min. A solution of alkyl halide (3.0 equiv.) in dry THF (800 μL) was injected slowly using a syringe pump over 10 min with the needle contacting the wall of the neck allowing the reagent to cool to the reaction temperature before it reached the reaction mixture by dripping along the flask wall. The well-stirred reaction was then kept at −78 °C until completion (progress was monitored by TLC), the solvent was evaporated, and the residue was analyzed by ^1H NMR to determine the diastereomeric excess. Further purification by flash column chromatography (silica gel, hexane/EtOAc = 5:1) afforded the corresponding major diastereomers **16a** and **17** and minor diastereomers **15a** and **18** (Table 2).

General Procedure B (with Additive). A solution of LDA (1.3 equiv) in THF (2.4 mL) was added dropwise over a period of 10 min to a solution of the iminolactone **14a** (0.60 mmol) at −78 °C. HMPA (520 μL, 5 equiv) or DMPU (360 μL, 5 equiv) was added to the previous mixture. The resulting mixture was stirred at −78 °C for another 50 min. A solution of alkyl halide (3 equiv) in dry THF (800 μL) was injected slowly using a syringe pump over 10 min with the needle contacting the wall of the neck allowing the reagent to cool to the reaction temperature before it reached the reaction mixture by dripping along the flask wall. The well-stirred reaction was then kept at −78 °C for another 50 min, the solvent was evaporated, and the residue was analyzed by ^1H NMR to determine the diastereomeric excess. Further purification by column chromatography (silica gel, hexane/EtOAc = 5:1) afforded the corresponding major diastereomers **16a** and **17** and minor diastereomer **15a** and **18** (Table 2).

(3*S*,6*R*)-3-Benzyl-6-(methoxymethyl)-3,6-dimethyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (16a). Yield: 132 mg (65%). Colorless oil. $[\alpha]^{23}_D = -37.1$ ($c = 5.24$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3030 (m), 2984 (s), 2929 (s), 1738 (s), 1666 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20−7.39 (m, 10H, Ph), 3.51 (d, $J = 13.2$ Hz, 1H, CH_2), 3.15 (d, $J = 12.8$ Hz, 1H, CH_2), 3.08 (d, $J = 10.8$ Hz, 1H, CH_2), 3.02 (d, $J = 10.4$, 1H, CH_2), 2.92 (s, 3H, OCH_3), 1.67 (s, 3H, CH_3), 1.47 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 165.8, 138.0, 136.4, 131.0, 128.9, 128.3, 127.7, 127.3, 126.6, 86.8, 75.7, 62.0, 59.0, 46.7, 28.6, 22.8. MS: *m/z* 337 (M^+, 5.8), 293 (27.3), 262 (25.7), 246 (19.9), 202 (94.3), 131 (56.2), 118 (33.6), 91 (100), 65 (15.5). HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$ M^+ 337.1678, found M^+ 337.1670. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.35; H, 6.93; N, 4.02.

(3*S*,6*R*)-3-Benzyl-3-ethyl-6-(methoxymethyl)-6-methyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (17a). Yield: 175 mg (83%). White solid. Mp = 42−44 °C. $[\alpha]^{23}_D = -50.0$ ($c = 0.70$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3029 (m), 2930 (s), 1736 (s), 1667 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22−7.42 (m, 10H, Ph), 3.47 (d, $J = 12.8$ Hz, 1H, CH_2), 3.16 (d, $J = 13.2$ Hz, 1H, CH_2), 3.04 (d, $J = 10.8$ Hz, 1H, CH_2), 2.96 (s, 3H, OCH_3), 2.82 (d, $J = 10.4$ Hz, 1H, CH_2), 2.22−2.31 (m, 1H, CH_2), 1.91−2.00 (m, 1H, CH_2), 1.43 (s, 3H, CH_3), 0.93 (t, $J = 7.6$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.9, 138.8, 136.3, 131.3, 129.0, 128.4, 127.8, 127.4, 126.8, 86.7, 75.9, 66.6, 59.1, 46.5, 34.2, 23.0, 9.3. MS: *m/z* 351 (M^+, 1.89), 307 (14.8), 276 (17.6), 216 (16.9), 131 (42.0), 115 (20.5), 91 (100), 77 (10.6). HRMS: *m/z* calcd for $C_{22}H_{25}NO_3$ M^+ 351.1834, found M^+ 351.1826. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.19; H, 7.05; N, 3.96.

(3*R*,6*R*)-3-Benzyl-3-ethyl-6-(methoxymethyl)-6-methyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (18a). Yield 25 mg (12%). White solid. Mp = 123−125 °C. $[\alpha]^{23}_D = +52.4$ ($c = 0.21$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3033 (m), 2970 (s), 2926 (s), 1728 (s), 1672 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21−7.39 (m, 10H, Ph), 3.42 (d, $J = 12.8$ Hz, 1H, CH_2), 3.28 (s, 3H, OCH_3), 3.24 (d, $J = 10.4$ Hz, 1H, CH_2), 3.10 (d, $J = 10.4$ Hz, 1H, CH_2), 3.09 (d, $J = 12.8$ Hz, 1H, CH_2), 2.36−2.45 (m, 1H, CH_2), 1.97−2.06 (m, 1H, CH_2), 0.96 (t, $J = 7.4$ Hz, 3H, CH_3), 0.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.0, 138.2, 136.3, 131.0, 129.0, 128.4, 128.2, 127.3, 127.3, 86.8, 76.0, 67.2, 58.9, 47.2, 34.5, 21.0, 9.0. MS: *m/z* 351 (M^+, 10.9), 307 (60.7), 276 (50.8), 216 (60.1), 161 (28.5), 131 (90.4), 117 (28.1), 91 (100). HRMS: *m/z* calcd for $C_{22}H_{25}NO_3$ M^+ 351.1834, found M^+ 351.1829. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.36; H, 6.96; N, 3.94.

2-[(3*R*,6*R*)-3-Benzyl-3,6-dihydro-6-(methoxymethyl)-6-methyl-2-oxo-5-phenyl-2*H*-1,4-oxazin-3-yl]acetonitrile (17b). Yield: 196 mg (90%). White solid. Mp = 152−154 °C. $[\alpha]^{23}_D = +50.3$ ($c = 0.73$, $CHCl_3$). IR (NaCl, $CHCl_3$): 3028 (m), 2990 (s), 2931 (s), 2248 (m), 1737 (s), 1665 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19−7.45 (m, 10H, Ph), 3.43 (d, $J = 13.2$ Hz, 1H, CH_2), 3.24 (s, 2H, CH_2), 3.21 (d, $J = 13.2$ Hz, 1H, CH_2), 3.17 (d, $J = 16.4$ Hz, 1H, CH_2), 3.10 (s, 3H, OCH_3), 2.89 (d, $J = 16.0$ Hz, 1H, CH_2), 1.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 167.9, 137.4, 134.0, 131.0, 129.3, 128.5, 128.1, 127.4, 127.2, 116.5, 88.1, 75.7, 62.9, 59.0, 45.9, 29.5, 23.4. MS: *m/z* 362 (M^+, 60.3),

271 (85.4), 91 (100). HRMS: *m*/*z* calcd for $C_{22}H_{22}N_2O_3$ M^+ 362.1630, found M^+ 362.1626. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.44; H, 6.12; N, 7.02.

2-[(3*R*,6*R*)-3-Benzyl-3,6-dihydro-6-(methoxymethyl)-6-methyl-2-oxo-5-phenyl-2*H*-1,4-oxazin-3-yl]acetonitrile (18b). Yield: 20 mg (9%). White solid. Mp = 76−78 °C. $[\alpha]^{23}_D$ = +73.4 (*c* = 0.94, $CHCl_3$). IR (NaCl, $CHCl_3$): 2930 (s), 2249 (m), 1732 (s), 1671 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18−7.45 (m, 10H, Ph), 3.42 (d, *J* = 12.8 Hz, 1H, CH_2), 3.32 (d, *J* = 10.0 Hz, 1H, CH_2), 3.32 (s, 2H, CH_2), 3.26 (d, *J* = 12.8 Hz, 1H, CH_2), 3.16 (s, 3H, OCH_3), 3.14 (d, *J* = 10.0 Hz, 1H, CH_2), 0.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 168.0, 137.3, 134.3, 130.9, 129.3, 128.5, 128.3, 127.8, 127.2, 115.9, 87.8, 75.8, 63.0, 59.0, 46.1, 29.4, 20.2. MS: *m*/*z* 362 (M^+, 42.3), 271 (65.2), 131 (26.9), 115 (42.5), 91 (100), 77 (15.2). HRMS: *m*/*z* calcd for $C_{22}H_{22}N_2O_3$ M^+ 362.1630, found M^+ 362.1629. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.48; H, 6.06; N, 7.05.

(3*S*,6*R*)-3-Allyl-3-benzyl-6-(methoxymethyl)-6-methyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (17c). Yield: 172 mg (79%). White solid. Mp = 67−68 °C. $[\alpha]^{23}_D$ = −58.0 (*c* = 0.54, $CHCl_3$). IR (NaCl, $CHCl_3$): 3068 (m), 2990 (s), 2927 (s), 1736 (s), 1670 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22−7.41 (m, 10H, Ph), 5.69−5.79 (m, 1H, CH), 5.23−5.26 (m, 2H, CH_2), 3.51 (d, *J* = 12.8 Hz, 1H, CH_2), 3.20 (d, *J* = 13.2 Hz, 1H, CH_2), 3.02 (d, *J* = 10.8 Hz, 1H, CH_2), 2.95 (dd, *J* = 13.2, 7.2 Hz, 1H, CH_2), 2.91 (s, 3H, OCH_3), 2.88 (d, *J* = 10.8 Hz, 1H, CH_2), 2.70 (dd, *J* = 13.2, 8.0 Hz, 1H, CH_2), 1.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 167.4, 138.0, 136.0, 132.5, 131.3, 129.1, 128.4, 127.8, 127.4, 126.8, 120.5, 86.8, 75.8, 66.0, 59.1, 46.3, 45.5, 23.1. MS: *m*/*z* 363 (M^+, 5.7), 319 (21.5), 288 (52.9), 131 (100), 91 (94.6). HRMS: *m*/*z* calcd for $C_{23}H_{25}NO_3$ M^+ 363.1834, found M^+ 363.1827. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.18; H, 6.65; N, 3.27.

(3*R*,6*R*)-3-Allyl-3-benzyl-6-(methoxymethyl)-6-methyl-5-phenyl-3*H*-1,4-oxazin-2(6*H*)-one (18c). Yield: 31 mg (14%). White solid. Mp = 117−118 °C. $[\alpha]^{23}_D$ = +30.7 (*c* = 0.14, $CHCl_3$). IR (NaCl, $CHCl_3$): 3067 (m), 2987 (s), 1724 (s), 1675 (ms) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21−7.40 (m, 10H, Ph), 5.81−5.92 (m, 1H, CH), 5.12−5.22 (m, 2H, CH_2), 3.44 (d, *J* = 12.8 Hz, 1H, CH_2), 3.28 (s, 3H, OCH_3), 3.25 (d, *J* = 10.4, 1H, CH_2), 3.15 (d, *J* = 12.8 Hz, 1H, CH_2), 3.10 (d, *J* = 10.4 Hz, 1H, CH_2), 3.04 (dd, *J* = 13.6, 8.4 Hz, 1H, CH_2), 2.84 (dd, *J* = 13.2, 7.2 Hz, 1H, CH_2), 0.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 166.7, 138.3, 136.1, 128.9, 128.4, 128.2, 127.3, 127.3, 118.2, 86.8, 76.0, 66.2, 59.0, 46.5, 45.8, 21.0. MS: *m*/*z* 363 (M^+, 40.7), 318 (25.6), 288 (29.1), 262 (31.8), 228 (22.8), 131 (90.1), 91 (100). HRMS: *m*/*z* calcd for $C_{23}H_{25}NO_3$ M^+ 363.1834, found M^+ 363.1836. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.10; H, 6.60; N, 3.25.

Hydrolysis of the Dialkylated iminolactones 15a−d, 16a, and 17c. Synthesis of Compounds 19a−d and *ent*-19a: General Procedure. Iminolactone (0.20 mmol) was dissolved in 8 N HCl aqueous solution (1 mL) in a sealed tube with a Teflon screw cap and heated at 90 °C. After the mixture was stirred for 1−3 h (progress was monitored by TLC), water (2 mL) was added, and the mixture was extracted with dichloromethane. The chiral auxiliary was recovered from the organic layer after removal of the solvent. The aqueous layer was evaporated under reduced pressure to give the desired α,α-disubstituted α-amino acid hydrochloride. The crude α-amino acid hydrochlorides were purified by recrystallization from a mixture of water and ethanol.

(*R*)-α-Methylphenylalanine Hydrochloride (19a). Yiled: 40 mg (92%). t_R = 7.2 min (HPLC). $[\alpha]^{23}_D$ = +9.40 (*c* = 0.73, H_2O) [lit.[4k] $[\alpha]_D$ = +9.50 (*c* = 0.2, H_2O)]. ^1H NMR (400 MHz, D_2O): δ 7.22−7.26 (m, 3H, Ph), 7.11−7.13 (m, 2H, Ph), 3.22 (d, *J* = 14.4 Hz, 1H, CH_2), 2.94 (d, *J* = 14.4 Hz, 1H, CH_2), 1.48 (s, 3H, CH_3).

(*S*)-α-Methylphenylalanine Hydrochloride (*ent*-19a). Yield: 39 mg (91%). t_R = 11.2 min (HPLC). $[\alpha]^{23}_D$ = +9.41 (*c* = 0.72, H_2O) [lit.[17] $[\alpha]^{25}_D$ = +9.60 (*c* = 0.2, H_2O)].

(*R*)-α-Methylaspartic Acid Hydrochloride (19b). Yield: 36 mg (98%). t_R = 15.4 min (HPLC). $[\alpha]^{23}_D$ = +36.2 (*c* = 0.83, MeOH) [lit.[18] $[\alpha]_D$ = +35.1 (*c* = 1.27, MeOH)]. ^1H NMR (400 MHz, D_2O): δ 3.06 (d, *J* = 16.8 Hz, 1H, CH_2), 2.79 (d, *J* = 18.0 Hz, 1H, CH_2), 1.44 (s, 3H, CH_3).

(*R*)-α-Allylalanine Hydrochloride (19c). Yield: 28 mg (85% yield). t_R = 6.2 min (HPLC). $[\alpha]^{23}_D$ = +13.4 (*c* = 0.57, D_2O) [lit.[5f] $[\alpha]_D$ = +14.4 (*c* = 1.3, D_2O) for (*S*)-isomer]. ^1H NMR (400 MHz, D_2O): δ 5.54−5.64 (m, 1H, CH), 5.11−5.15 (m, 2H, CH_2), 2.55 (dd, *J* = 14.4, 6.8 Hz, 1H, CH_2), 2.40 (dd, *J* = 14.4, 8.0 Hz, 1H, CH_2), 1.40 (s, 3H, CH_3).

(*S*)-α-Allylphenylalanine Hydrochloride (19d). Yield: 39 mg (80% yield). t_R = 14.1 min (HPLC). $[\alpha]^{23}_D$ = +15.3 (*c* = 0.78, H_2O) [lit.[19] $[\alpha]_D$ = +16.0 (*c* = 1.0, 1 M HCl)]. ^1H NMR (400 MHz, D_2O): δ 7.20−7.25 (m, 2H, Ph), 7.09−7.11 (m, 2H, Ph), 5.55−5.66 (m, 1H, CH), 5.11−5.16 (m, 2H, Ph), 3.21 (d, *J* = 14.4 Hz, 1H, CH_2), 2.90 (d, *J* = 14.4 Hz, 1H, CH_2), 2.68 (dd, *J* = 14.0, 8.0 Hz, 1H, CH_2), 2.41 (dd, *J* = 14.4, 8.4 Hz, 1H, CH_2).

Acknowledgment. Financial support by the National Science Council of the Republic of China is gratefully acknowledged.

Supporting Information Available: X-ray position parameters, full bond distances and angles, and an ORTEP drawing for **15a** and tables of total energies and Cartesian coordinates for the minimized structure by AM1 and ab initio calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801514G

(17) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286.
(18) Crich, D.; Chan, C.-O.; Natarajan, S. *Tetrahedron Lett.* **1992**, *33*, 3405–3408.
(19) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460–2470.