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Diastereoselective Synthesis of β-Substituted-α,γ-Diaminobutyric Acids and Pyrrolidines Containing Multichiral Centers

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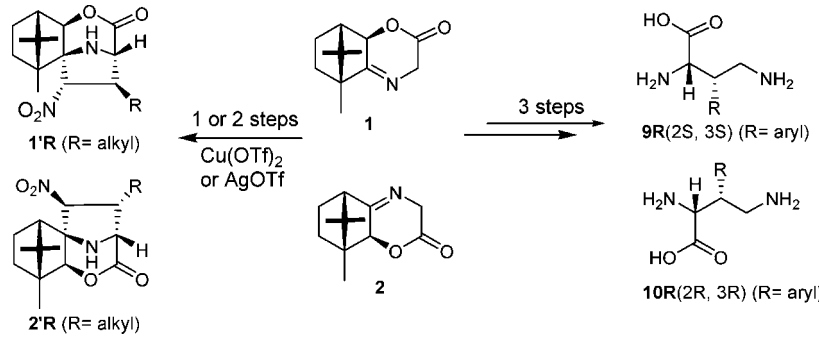

A convenient and efficient way for the highly diastereoselective synthesis of β-substituted-α,γ-diaminobutyric acids and pyrrolidines containing multichiral centers has been well-developed. Michael addition of chiral tricyclic iminolactones **1** and **2** to nitroalkenes afforded the adducts in good yields (up to 95%) and excellent diastereoselectivities (up to dr > 99:1) when titanium(IV) isopropoxide was used. Configuration of the second new stereocenter was decided by the substitution of nitroalkene. Selective reduction and hydrolysis of the Michael adducts furnished the desired β-substituted-α,γ-diaminobutyric acids in good yields and high enantiomeric excesses (>99% ee). Synthesis of pyrrolidines containing multichiral centers has also been accomplished in good to excellent yields and diastereoselectivities under mild conditions via Michael−Mannich tandem reactions using $Cu(OTf)_2$ or AgOTf as an activating reagent for aliphatic nitroalkenes.

Introduction

Optically active nonproteinogenic amino acids have received considerable attention for their nutritional, biological, and chemical importance.[1,2] As a member of this class of compounds, α,γ-diaminobutyric acid (DABA) was first identified in *Polygonatum multiflorum*[3] and subsequently isolated from *Lathyrus latifolius* by Ressler et al.,[4] who demonstrated its acute neurotoxicity in rats. O'Neal et al.[5] discovered that DABA, a lower homologue of ornithine, induced ammonia toxicity in rats by inhibiting the liver enzyme ornithine transcarbamylase and disrupting the urea cycle. DABA appeared to be found in the chick brain and excreta[6] to have antitumor activities in vitro and in vivo against mouse fibrosarcoma cells.[7] 3-Amino-2-pyrrolidones are derivatives of α,γ-diaminobutyric acids and are of interest as pharmaceutically important peptides.[8] Although α,γ-diaminobutyric acids possess wide biological activities, little

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attention was paid probably due to the lack of a general method for their syntheses.

Pyrrolidines are of the important class of five-membered heterocycles, which not only are common structural subunits present in natural and unnatural products[9] but also are widely used as chiral auxiliaries in asymmetric organic synthesis.[10] Depending on the substitution pattern and functionalization, pyrrolidines have been reported to possess different important biological activities. They can act as antibacterials,[11] neuroexcitatory agents,[12] glycosidase inhibitors,[13] and fungicides.[14] However, their construction with predictable regio- and stereocontrol still constitutes a challenge in organic chemistry.

Michael addition of electron-deficient olefins is without question one of the most classical and fundamental carbon−carbon bond formation reactions.[15,16] Nitroalkenes have been attracting continuous attention as electron acceptors because the nitro group can only lead to 1,4-addition as a result. This reaction and its similar variants have been extensively used in organic synthesis.[17] Thus, it is not surprising that the development of enantioselective catalytic protocols for this reaction has received much attention.[16d−k] The chiral auxiliary methods are attractive approaches to stereocontrolling in such reactions. Important examples involved the stereocontrolled Michael addition of chiral glycine-derived enolates to electron-poor olefins.[18] Tricyclic iminolactones[19a] could act as effective equivalents of chiral amino acids in Michael addition reactions to nitroalkenes, thus allowing the convenient synthesis of enantiomerically enriched α,γ-diaminobutyric acids after subsequent manipulation of the nitro group and removal of the camphor-based protecting group. This process leads to the generation of up to two new stereogenic centers in the product.

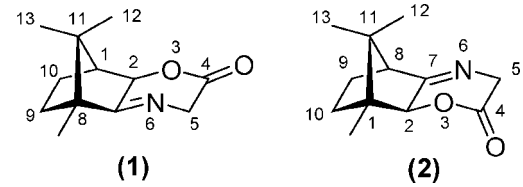

FIGURE 1. Tricyclic iminolactones **1** and **2**.

In this study, we focused our attention on the convenient asymmetric synthesis of the optically active β-substituted-α,γ-diaminobutyric acids via Michael addition followed by hydrolysis. In addition, high diastereoselectivity was obtained in the synthesis of pyrrolidines containing multichiral centers via Michael−Mannich tandem reaction in the presence of $Cu(OTf)_2$ or AgOTf.

Results and Discussion

Recently, we reported the synthesis of two novel chiral tricyclic iminolactones, (1*S*,2*R*,8*R*)-8,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.$0^{2,7}$]undec-6-en-4-one (**1**) and (1*R*,2*S*,8*S*)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6. 2.1.$0^{2,7}$]undec-6-en-4-one (**2**), prepared from (1*R*)-(+)-camphor as glycine equivalents, which have been successfully applied to the asymmetric synthesis of α-monosubstituted-α-amino acids, α,α-disubstituted-α-amino acids, and α,β-diamino acids.[19] Nitroalkenes,[20] as electron-deficient alkenes, were easily prepared via Henry reaction and subsequent dehydration procedure, which could be ideal acceptors for these two iminolactones **1** and **2** to prepare α,γ-diaminobutyric acids (Figure 1).

In order to find the experimental conditions most suitable for Michael addition, chiral tricyclic iminolactone (**1**) as the nucleophile and *trans*-β-nitrostyrene (**a**) as the Michael acceptor were selected at first for our model reactions. Representative results are listed in Table 1. To maximize diastereoselectivity, we performed the reaction at −78 °C as we did before.[19] Considering the solvent effect,[21] different solvents in the presence of LiCl and LDA were examined initially. The results showed that THF gave good diastereoselectivity and conversion rate compared with dichloromethane and toluene (entries 1−3). The effects of base and additives were also investigated. Specifically, both *n*-BuLi and LHMDS in THF afforded poor diastereoselectivities (dr 62:38 in LHMDS and dr 59:41 in

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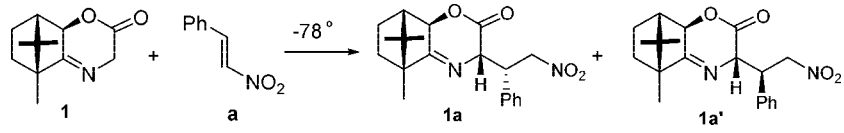
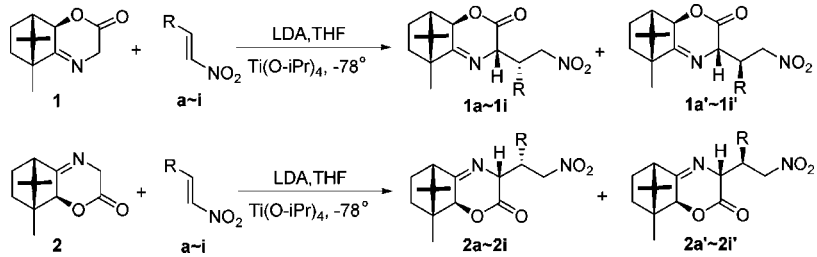
TABLE 1. Optimization on the Asymmetric Michael Addition of Tricyclic Iminolactone (1) to *trans*-β-Nitrostyrene (a)



entry	solvent	additive	base	conversion (%)[a]	dr[a]
1	THF	LiCl (6 equiv)	LDA	100	98:2
2	CH_2Cl_2	LiCl (6 equiv)	LDA	32	45:55
3	toluene	LiCl (6 equiv)	LDA	50	33:67
4	THF	LiCl (6 equiv)	LHMDS	100	62:38
5	THF	LiCl (6 equiv)	*n*-BuLi	59	59:41
6	THF	LiCl (10 equiv)	LDA	92	93:7
7	THF	$ZnCl_2$ (3 equiv)	LDA	78	96:4
8	THF	$MgBr_2$ (1.2 equiv)	LDA	63	74:26
9	THF	Ti (O-^{i}Pr)$_4$ (2.5 equiv)	LDA	100	>99:1

[a] By 400 MHz ^{1}H NMR of the crude products.

TABLE 2. Michael Addition of Tricyclic Iminolactones 1 and 2 to Aromatic Nitroalkenes



entry	R	adducts	dr (*syn*/*anti*)[a]	yield (%)[b]	> adducts	dr (*syn*/*anti*)[a]	yield (%)[b]
1	Ph	**1a**	>99:1	90	**2a**	>99:1	90
2	*p*-Cl-Ph	**1b**	>99:1	77	**2b**	96:4	77
3	*p*-OCH_3-Ph	**1c**	98:2	88	**2c**	>99:1	95
4	*o*-Cl-Ph	**1d**	>99:1	77	**2d**	98:2	82
5	*o*-OCH_3-Ph	**1e**	98:2	79	**2e**	98:2	78
6	*p*-$N(Me)_2$-Ph	**1f**	>99:1	72	**2f**	97:3	79
7	*p*-CH_3-Ph	**1g**	>99:1	91	**2g**	>99:1	82
8	*o*-CH_3-Ph	**1h**	>99:1	76	**2h**	>99:1	79
9	*m*-Cl-Ph	**1i**	96:4	74	**2i**	98:2	78

[a] By 400 MHz ^{1}H NMR of the crude products. [b] Yield of the major products after silica gel column chromatography.

n-BuLi, entries 4 and 5). As a metal-mediated reaction, we reasoned that the metal chelation could be used as a way to control stereoselectivity. Lithium enolate might often serve as a chelating metal cation in ethereal solvents at relatively low temperature. In an effort to enhance the stability of the chelate, we examined other common metal cations such as Zn(II), Mg(II), and Ti(IV).[22] On the basis of the experiments, readily accessible titanium(IV) isopropoxide [Ti(O-*i*Pr)$_4$] emerged as an effective additive (entries 6−9). Finally, entry 9 gave the optimum conditions for this Michael addition.

With the optimum conditions in hand, the scope of the reaction was investigated and a range of readily prepared aromatic nitroalkene acceptors were treated with chiral tricyclic iminolactones **1** and **2**. Observations of the reactions are summarized in Table 2. Compared with the aromatic nitroalkenes, the reaction system is relatively complex when treated with aliphatic substrates in the normal feeding order. As a result, we change the addition order of the reagents to improve the effectiveness of the target Michael addition reaction, satisfactory diastereoselectivity and yield were obtained as a result according to the optimum conditions used in entry 9 (Table 1) except feeding order. The results are listed in Table 3. Compared with the aromatic nitroalkenes, the reaction system is relatively complex when treated with aliphatic substrates. So we only changed the feeding order in order to improve the effectiveness of the target Michael addition reaction. Satisfactory diastereoselectivity and yield were obtained when we conducted the reaction with reversed feeding order (the reaction mixture was added into solution of nitroalkene). The results are listed in Table 3.

The configurations of the major Michael adducts, such as compounds **1a**, **2a**, **2g**, **2h**, and **2i**, which were obtained from aromatic substituted nitroalkenes, were unambiguously confirmed by X-ray crystallographic determination and obtained by recrystallization from a mixture of ethyl acetate and hexane

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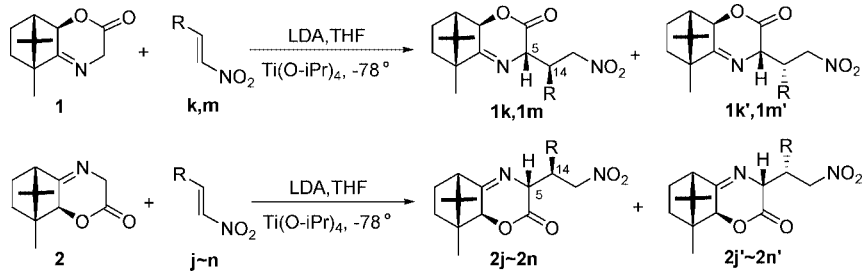
TABLE 3. Michael Addition of Tricyclic Iminolactones 1 and 2 to Aliphatic Nitroalkenes



entry	R	adducts	dr (*anti*/*syn*)[b,c]	yield (%)[b]
1	$(CH_2)_5$	**1m**	>99:1	93
2	$C(CH_3)_3$	**1k**	94:6	76
3	$CH(CH_3)_2$	**2j**	95:5	83
4	$C(CH_3)_3$	**2k**	93:7	71
5	(*S*)-2,2-dimethyl-1,3-dioxolane-4-yl	**2l**	>99:1	92
6	$(CH_2)_5$	**2m**	>99:1	92
7	cyclohexyl	**2n**	94:6	78

[a] By 400 MHz ^{1}H NMR of the crude products. [b] Yield of the major products after silica gel column chromatography. [c] Reversed addition (see Experimental Section).

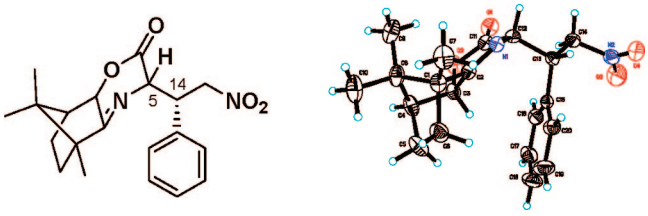


FIGURE 2. X-ray structure of compound **1a**.

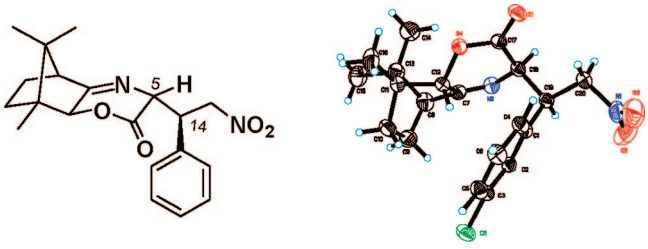


FIGURE 3. X-ray structure of compound **2i**.

(Figures 2 and 3).[23] Thus, compound **1** has a (5*S*,14*S*)-configuration, and compound **2** has a (5*R*,14*R*)-configuration. The configuration of aliphatic substituted Michael adducts was determined by the crystal structure of compound **2′j** because there was no configuration transformation at C14 in the reaction of compound **2j** to compound **2′j**. Compared to the *R*-configuration at C14 in compound **2′j**, we can deduce that the compound **2j** has the *S*-configuration at C14 according to the CIP sequence rules (see Scheme 3). Thus, compound **2j** has a (5*R*,14*S*)-configuration.

On the basis of these observations, there are strong correlations between the enolate geometries and the adduct stereostructures. Predominantly *syn* adducts were obtained when R substitution was an aryl group, which is in agreement with the results of other workers in this field.[16b,j] On the other hand, *anti* adducts were preferentially formed when aliphatic nitroalkenes were used. To our satisfaction, good to excellent diastereomeric ratios were obtained. The mechanism for the Michael

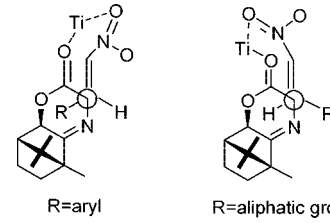


FIGURE 4. Proposed mechanism of Michael addition of **1** with aromatic and aliphatic nitroalkenes.

addition of tricyclic iminolactone to (*E*)-nitroalkene was proposed to involve a chelated eight-membered transition state. Similar concepts were proposed by Heathcock's group,[24] Ley's group,[16c] and Schollkopf's group.[22]

In our studies, the extremely high *endo*/*exo* ratio at the C5 position in the tricyclic iminolactone is presumably due to the steric hindrance of C12-methyl substitution and/or the interaction between the lone-pair electron of the imine and the electrophile, which effectively hinders the orientation from the *exo* face and thus favors the attack of the electrophile from the *endo* face of the enolate (*endo*/*exo* > 99:1).[19] Noticeably, *syn* adducts (R = aromatic group) and *anti* adducts (R = aliphatic group) were obtained with high diastereoselectivities in our experiments. The reason for the difference probably can be described as the proposed mechanisms in Figure 4. There is $\pi-\pi$ interaction between the aromatic group of the acceptor and the π-system of N=C in the donor, so the *syn* adducts were favored for aromatic nitroalkenes. The mechanism can be further supported by the chemical shift of C2−H in tricyclic iminolactone. The shielding effect of the aromatic ring makes the C2−H of the Michael adduct shift to a higher field compared with that in compounds **1** and **2**. However, there is no $\pi-\pi$ interaction in the case of aliphatic nitroalkene, thus the *anti* adduct was correspondingly generated in order to reduce the steric interaction.

The ultimate goal of most applications of nitroalkane chemistry involves further conversion of the nitro unit, most commonly by reduction to give a primary amine. Reductive manipulation of the nitro group is necessary to confirm the effectiveness of this reaction as an asymmetric method for the

(23) The X-ray crystallographic structures of compounds **1a**, **2a**, **2g**, **2h**, and **2i** have been submitted to the Cambridge Crystallographic Data Centre. The CCDC numbers for compounds **1a**, **2a**, **2g**, **2h**, and **2i** are CCDC 678006, CCDC 678011, CCDC 678012, CCDC 678007, and CCDC 678013, respectively.

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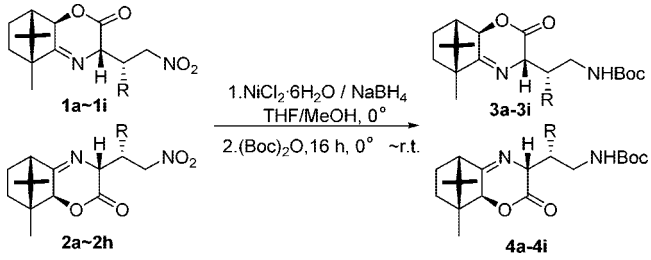
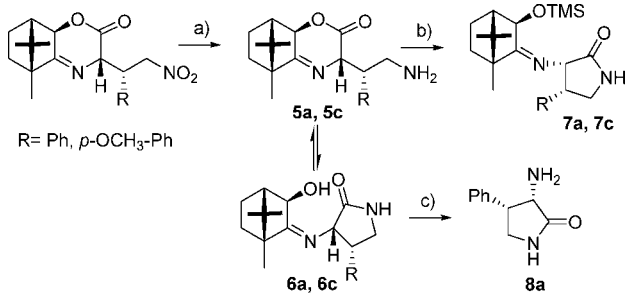
SCHEME 1. Reductive Manipulation of Michael Adducts to 3a−3i and 4a−4i



SCHEME 2. Manipulation of Michael Adducts to γ-Lactams 7 and 8[a]



[a] Reaction conditions: (a) $NiCl_2 \cdot 6H_2O/NaBH_4$, THF/MeOH, 0 °C to rt; (b) TMSOTf, *i*-Pr_2EtN, CH_2Cl_2, 0 °C; (c) 2 N HCl/THF, 50−60°C.

synthesis of α,γ-diaminobutyric acids while not affecting on the imine group in tricyclic iminolactone. The majority of such reductive procedures involves a transition metal catalyst, usually palladium, and a source of hydrogen, usually hydrogen gas.[25,26] Unfortunately, these reductions usually proceed slowly, thereby resulting in loss of stereochemical integrity and degradation of the substrate. It was eventually found that the most reliable way to reduce the nitro group with little effect on the imine was one-pot nickel borohydride reduction by carefully controlling the reaction temperature followed by the addition of di-*tert*-butyldicarbonate (Boc_2O) to the reaction system (Scheme 1).[27]

Before Boc_2O was added to the reduction system, we monitored the γ-lactam **6** in addition to the amino compound **5** when the reaction mixture was allowed to warm to room temperature. The equilibrium could not be destroyed until TMSOTf was added as a protecting reagent. The compound **7** was obtained in almost quantitative yield (Scheme 2).

Removal of the chiral auxiliary was achieved by hydrolysis of **3** and **4** in 4 N HCl solution at 50 °C for 2 h, which afforded the corresponding β-substituted-α,γ-diaminobutyric acids **9a**, **9c**, **9g**, **10a**, **10c**, and **10g** in good yields and excellent enantiomeric excesses (Table 4). The corresponding γ-lactam **8a** was also given after similar hydrolysis (Scheme 2).

Noticeably, pyrrolidine structures were detected simultaneously when aliphatic nitroalkenes were used in Michael addition (Scheme 3). The structures and the configurations of compounds were confirmed by X-ray crystallographic determination.[28] The observation from crystal structures of compound **2′j** showed that the partially eclipsed conformations were obtained at C5−C14 and C14−C15 in the pyrrolidine structure for the interpretation of the rigid structure of the fused rings (see Supporting Information). As a result, compound **2′R** has a (5*R*,14*R*)-configuration and **2′R′** has a (5*R*,14*S*)-configuration.

Although pyrrolidines are very useful, a direct approach to synthesize multichiral pyrrolidine is rather limited. Consquently, searching for an efficient Michael−Mannich tandem reaction to carry out the conversion of Michael adducts to multichiral pyrrolidine is still a very significant work. Up to now, considerable attention has been mainly focused on [3 + 2] annulations[29] or 1,3-dipolar cycloadditions[30] for pyrrolidine constructions. In order to obtain pyrrolidines from Michael adducts directly, a series of experiments were carried out by optimizing the experimental conditions in our laboratory, including the use of Et_3N, K_2CO_3, Triton B, NaH, DBU, and *t*-BuLi as base under different conditions. Unfortunately, pyrrolidines could not be synthesized successfully in the above-mentioned conditions.

We finally considered that the nonactivated imine group in tricyclic iminolactone might be the problem. Investigation results of recent literature relevant to catalytic nitro-Mannich reactions revealed that the use of chiral catalysts[31] or Lewis acid activated method[32] might be very helpful for this asymmetric Mannich-type reaction. Gratifyingly, the use of $Cu(OTf)_2$ or AgOTf as the activating reagent for an imine provided the expected Michael−Mannich tandem reaction product with almost quantitative yield and high diastereoselectivity (Scheme 4).

Conclusion

In summary, an efficient way for the synthesis of enantioenriched β-substituted-α,γ-diaminobutyric acids and their derivatives has been well-developed via Michael addition of chiral tricyclic iminolactones **1** and **2** as glycine equivalents to

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(28) The X-ray crystallographic structures of compounds **2′j** and **2′j′** have been submitted to the Cambridge Crystallographic Data Centre. The CCDC numbers for compounds **2′j** and **2′j′** are CCDC 678009 and CCDC 709779, respectively.

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SCHEME 3. Pyrrolidines Detected in the Aliphatic Nitroalkene-Mediated Michael Addition

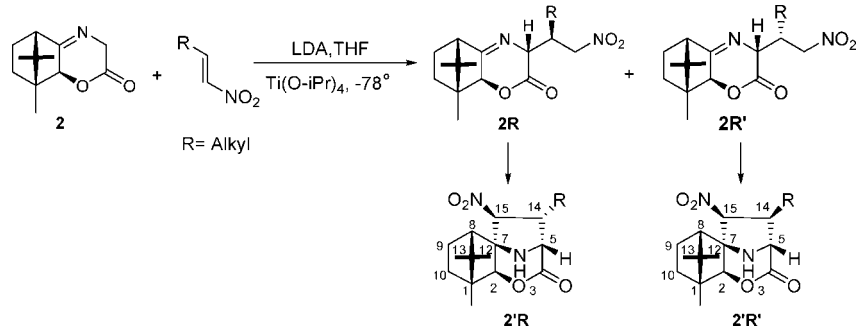
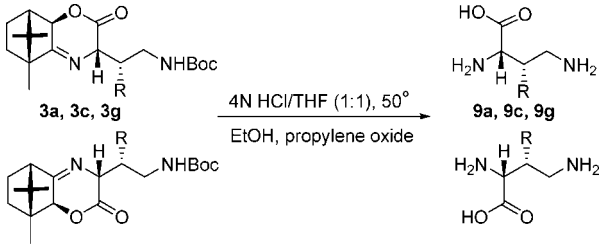


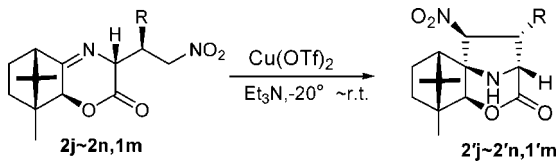
TABLE 4. Hydrolysis of the Derivatives of Michael Adducts to β-Substituted-α,γ-Diaminobutyric Acids 9 and 10



entry	substrate	R	product	yield (%)[a]	ee (%)[b]
1	**3a**	Ph	**9a**	82	>99
2	**3c**	*p*-OCH_3-Ph	**9c**	78	>99
3	**3g**	*p*-CH_3-Ph	**9g**	68	>99
4	**4a**	Ph	**10a**	65	>99
5	**4c**	*p*-OCH_3-Ph	**10c**	79	>99
6	**4g**	*p*-CH_3-Ph	**10g**	67	>99

[a] Isolated yield. [b] Enantiomeric excess (%) values are determined by HPLC analysis utilizing a CR(+) column.

SCHEME 4. $Cu(OTf)_2$ as Lewis Acid in the Synthesis of Pyrrolidines



nitroalkenes with subsequent hydrolysis of Michael adducts. Addition of titanium(IV) isopropoxide, instead of lithium chloride, yielded better selectivity. Moreover, it was noticed that the configurations of the products depended on the substitutions of nitroalkenes. On the basis of the above reaction, pyrrolidines containing multichiral centers via Michael−Mannich tandem reaction have also been accomplished using $Cu(OTf)_2$ or AgOTf as the activating reagent. Good to excellent yields and diastereoselectivities were obtained under mild conditions. Studies on Lewis acid catalytic Michael−Mannich tandem reactions to construct the pyrrolidines by applying other imines are in progress.

Experimental Section

General Procedure for the Michael Addition of Tricyclic Iminolactones to Aromatic Nitroalkenes (1a−1i and 2a−2i): Diisopropylamine (0.156 mL, 1.1 mmol, 1.1 equiv) was added to a solution of dry THF (1.0 mL) and *n*-BuLi (1.6 M, 0.688 mL, 1.1 mmol, 1.1 equiv) at −30 °C, and the mixture was stirred for 30 min under an argon atmosphere. A solution of iminolactone (0.207 g, 1.0 mmol) in dry THF (10.0 mL) was added dropwise over a period of 10 min to the above freshly prepared LDA solution via a syringe at −30 °C. A solution of $Ti(O\text{-}iPr)_4$ (0.370 mL, 2.5 mmol, 2.5 equiv) in dry THF (2.0 mL) was added after the reaction mixture was cooled to −78 °C. A solution of nitroalkenes (1.05 mmol, 1.05 equiv) in dry THF (10.0 mL) was then added via a syringe over 10 min. The well-stirred reaction was kept at −78 °C for 2 h. The reaction was quenched at −78 °C by the addition of saturated NH_4Cl (2.0 mL). The reaction mixture was then allowed to warm to room temperature and filtered. The filtrate was extracted with EtOAc (3 × 15.0 mL), and the combined extracts were washed with water (3 × 3.0 mL) and brine (3 × 3.0 mL), dried over anhydrous $MgSO_4$, and then concentrated to give the crude product. The crude product was purified by flash column chromatography to yield the desired compound.

(1*S*,2*R*,5*S*,8*R*)-5-((*S*)-1-Phenyl-2-nitroethyl)-8,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.$0^{2,7}$]undec-6-en-4-one (1a): Purified by chromatography (EtOAc/petroleum = 1/4), white solid, mp 208−210 °C; $[\alpha]^{20}_D$ = +48 (*c* = 0.85, CH_2Cl_2); FT-IR (KBr) 3380 (br), 1728 (s), 1694 (m), 1549 (vs), 1377 (m), 1029 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.32 (m, 3H), 7.17−7.14 (m, 2H), 5.18−5.07 (m, 2H), 4.77 (d, *J* = 4.0 Hz, 1H), 4.07−4.02 (m, 1H), 2.37(s, 1H), 1.85 (d, *J* = 4.8 Hz, 1H), 1.82−1.76 (m, 1H), 1.63−1.56 (m, 1H), 1.33−1.26 (m, 1H), 1.02 (s, 3H), 0.84 (s, 3H), 0.68 (s, 3H), 0.65−0.61 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 169.4, 134.5, 129.3, 129.0, 128.4, 79.2, 76.4, 63.8, 52.9, 48.3, 47.2, 45.3, 28.8, 25.8, 19.9, 19.4, 10.1 ppm; MS *m*/*z* 356 (M^+, 1.9), 341 (1.3), 328 (2.5), 312 (1.3), 297 (2.2), 284 (2.1), 266 (2.1), 252 (1.5), 238 (2.3), 206 (13.6), 178 (100.0), 162 (12.0), 150 (23.6), 110 (37.4), 104 (66.5), 91 (52.0), 77 (45.5), 69 (79.0), 55 (29.1), 41 (76.6); HRMS (ESI) calcd for $C_{20}H_{25}N_2O_4$ $[M + H]^+$ 357.1809, found 357.1805.

General Procedure for the Michael Addition of Tricyclic Iminolactones to Aliphatic Nitroalkenes (1m and 2j−2n): Metal chelate's formation was the same as the above procedure, and it was then slowly transferred to a solution of nitroalkene in dry THF in a long-necked flask under stirring at −78 °C with a double-sided needle. The well-stirred reaction was kept at −78 °C for 2 h and then worked up as above. The crude product was purified by flash column chromatography to yield the desired compound.

2j (5*R*,14*S*): Purified by chromatography (EtOAc/petroleum = 1:10−1:6), white solid, mp 144−146 °C, $[\alpha]^{20}_D$ = −148 (*c* = 0.49, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (d, *J* = 7.6 Hz, 1H), 4.73 (s, 1H), 3.58 (s, 1H), 2.61 (br, 1H), 2.59 (s, 1H), 2.04 (d, *J* = 4.0 Hz, 1H), 1.68−1.60 (m, 1H), 1.57−1.50 (m, 1H), 1.40−1.34 (m, 1H), 1.17 (s, 3H), 1.02 (s, 3H), 1.00−0.97 (m, 1H), 0.95 (s, 9H), 0.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 89.1, 83.1, 72.6, 57.5, 56.9, 52.1, 50.5, 50.1, 33.4, 33.3, 26.4, 22.9, 21.5, 20.4, 10.6 ppm; HRMS (ESI) calcd for $C_{17}H_{27}N_2O_4$ $[M + H]^+$ 323.1965, found 323.1969.

General Procedure for the Michael−Mannich Tandem Reaction to Generate Pyrrolidines (1′m and 2′j−2′n): The crude Michael adduct was dissolved in THF (5.0 mL) and cooled to −20 °C. $Cu(OTf)_2$ (10% mmol) was added with efficient stirring under

argon flow protection to result in a green solution. Then Et_3N (1.0 equiv) was added after 30 min, and the reaction mixture was stirred at −20 °C for 2 h before allowing it to warm to room temperature. The catalyst was removed by filtration, and the crude product after concentration was purified by flash column chromatography (petroleum/ethyl acetate = 30:1−12:1) to get the desired compound.

2′j (5*R*,7*S*,14*R*,15*S*): Purified by chromatography (EtOAc/petroleum = 1:30−1:12), white solid, mp 211−213 °C, $[\alpha]^{20}_D$ = −85.0 (c = 1.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, J = 8.8 Hz, 1H), 3.81 (m, 1H), 3.59 (d, J = 5.2 Hz, 1H), 3.38 (s, 1H), 2.22−2.16 (m, 1H), 1.91−1.85 (m, 1H), 1.82 (d, J = 4.0 Hz, 1H), 1.77−1.68 (m, 1H), 1.63−1.57 (m, 1H), 1.54 (s, 1H), 1.25 (s, 3H), 1.08 (d, J = 8.4 Hz, 3H), 1.01 (s, 3H), 0.93 (d, J = 8.4 Hz, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 93.5, 89.3, 61.7, 56.1, 50.7, 49.7, 49.1, 34.3, 28.6, 22.9, 22.4, 22.2, 21.9, 21.6, 10.6 ppm; HRMS (ESI) calcd for $C_{17}H_{27}N_2O_4$ $[M + H]^+$ 323.1965, found 323.1968.

General Procedure for the Selective Reduction of Michael Adducts (3a−3i and 4a−4i): The nitro compound (**1a**−**1i** or **2a**−**2i**, 0.1 mmol) was dissolved in THF (1.5 mL) and MeOH (0.7 mL) at ambient temperature, and $NiCl_2 \cdot 6H_2O$ (48 mg, 0.2 mmol, 2 equiv) was added under argon flow. After the mixture was stirred for 20 min, it was cooled to 0 °C. Then $NaBH_4$ (24 mg, 0.6 mmol, 6 equiv) was added in small portions to result in a black solution, and the mixture was stirred at 0 °C for 3 h before the addition of Boc_2O (66 mg, 0.3 mmol, 3 equiv). The solution was allowed to warm to room temperature and stirred for 16 h. The mixture was filtered through a short silica gel column eluting with EtOAc to remove the black precipitate. The eluent was concentrated, and the residue was purified by flash column chromatography to give the desired compound.

(1*S*,2*R*,5*S*,8*R*)-5-((*S*)-*N*-*tert*-Butoxycarboxyl-1-phenyl-2-aminoethyl)-8,11,11-trimethyl-3-oxa-6-aza-tricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (3a): Purified by chromatography (EtOAc/petroleum = 1:4−1:3), colorless oil, $[\alpha]^{20}_D$ = +21.0 (c = 1.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.09 (m, 2H), 5.05 (br s, 1H), 4.84 (d, J = 3.6 Hz, 1H), 3.81−3.71 (m, 2H), 3.41 (m, 1H), 2.29 (s, 1H), 1.81 (d, J = 3.6 Hz, 1H), 1.79−1.70 (m, 1H), 1.58−1.46 (m, 1H), 1.39 (s, 9H), 1.29−1.23 (m, 1H), 0.99 (s, 3H), 0.81 (s, 3H), 0.66 (s, 3H), 0.59−0.54 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 170.1, 155.7, 137.6, 128.8, 127.9, 79.3, 79.0, 63.8, 52.6, 48.1, 47.7, 47.3, 42.0, 29.0, 28.3, 25.8, 19.9, 19.3, 10.1 ppm; HRMS (ESI) calcd for $C_{25}H_{35}N_2O_4$ $[M + H]^+$ 427.2591, found 427.2594.

General Procedure for Preparation of 9 and 10: Compound **3** or **4** (0.14 mmol) was dissolved in 4 N HCl (1.0 mL) in a sealed tube with a Teflon screw cap and heated at 50 °C for 2 h. After the mixture was cooled to room temperature, water (1.0 mL) was added, and the mixture was extracted with diethyl ether. The aqueous layer was evaporated under reduced pressure, and the residue was dissolved in EtOH (1.0 mL). Propylene oxide (0.5 mL) was then added, and the mixture was stirred at room temperature for 30 min during which time the white solid started to precipitate. The precipitate was collected by filtration and washed successively with cold EtOH and Et_2O to afford the desired amino acid.

(2*S*,3*S*)-2,4-Diamino-3-phenylbutanoic Acid (9a): White solid, mp 232 °C (dec.); $[\alpha]^{20}_D$ = −11.0 (c = 0.25, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 7.18 (m, 3H), 7.05 (m, 2H), 3.70 (d, J = 4.8 Hz, 1H), 3.49 (dd, J = 8.4 Hz, J = 12.8 Hz, 1H), 3.29 (dd, J = 4.4, 12.8 Hz, 1H), 3.21 (m, 1H) ppm; HRMS (ESI) calcd for $C_{10}H_{15}N_2O_2$ $[M + H]^+$ 195.1128, found 195.1128. Ee >99%, determined by HPLC.

Acknowledgment. We are grateful for the financial support of the National Natural Science Foundation of China (NSFC, 20772051, 20572039), the Program for NCET-05-0880, and the Doctoral Funds from the Chinese Ministry of Education of the People's Republic of China.

Supporting Information Available: X-ray structure of **1a**, **2a**, **2g**, **2h**, **2i**, and **2′j** (major) (CIF), synthesis, characterization, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and HPLC results. This material is available free of charge via the Internet at http://pubs.acs.org.

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