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Palladium(II)-Catalyzed Asymmetric Synthesis of (*Z*)-α-Alkylidene-γ-butyrolactams from (*Z*)-*N*-Allylic 2-Alkynamides. Total Synthesis of (−)-Isocynometrine

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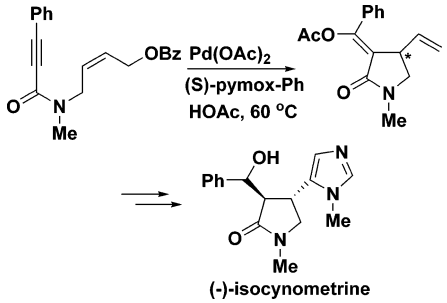
Received February 11, 2006



$Pd(OAc)_2$ combined with nitrogen-containing ligands catalyzed the cyclization of (*Z*)-*N*-allylic 2-alkynamides in acetic acid to afford the α-(*Z*)-acetoxyalkylidene-γ-butyrolactams in high yield and high stereoselectivity. When chiral nitrogen-containing ligands were used, the catalytic asymmetric protocol was achieved with moderate enantioselectivity (up to 80 °C). The utility of this new methodology was exemplified by the total synthesis of (−)-isocynometrine.

Introduction

γ-Butyrolactam structures are widely spread in medicinal chemistry.[1] In particular, α-alkylidene-γ-butyrolactams show important biological activities, such as cytotoxicity,[2] antitumor,[3] and antiinflamation activities but with lower toxicity[4] as compared with the corresponding lactones. Therefore, the development of new methods for the stereoselective synthesis of these kinds of molecules appears to be highly desirable.

The use of transition metal catalysts in the carbocyclization of alkenes and alkynes offers the unique means to construct a variety of synthetically important carbo- and heterocycles with high efficiency not normally accessible by traditional methods.[5] Recently, we have developed the facile intramolecular enyne cyclization of allylic 2-alkynoates or *N*-allylic 2-alkynamides to build polysubstituted α-alkylidene-γ-butyrolactones[6] or α-alkylidene-γ-butyrolactams[7,8] via a Pd(II) catalyst, initiated by halopalladation. In these reactions, halide ions serve not only as nucleophiles but also as a ligand to inhibit the β-hydride elimination reaction.[9] However, there exist problems in the way of developing the corresponding catalytic asymmetric process while halides are used as a ligand. To solve these problems, a new type of reaction to construct α-alkylidene-γ-butyrolactones

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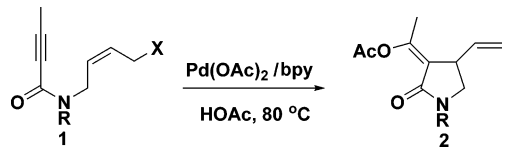
10.1021/jo060288w CCC: $33.50
Published on Web 04/21/2006

TABLE 1. Cyclization of *N*-(*Z*)-(4′-X-2′-butenyl)-2-butynamides (X = leaving group)[a]



	substrate					
entry[a]	R	X		time (h)	product[b]	yield (%)[c,d]
1	H	OBz	**1a**	24	**2a**	*e*
2	Me	OBz	**1b**	28	**2b**	70
3	Bn	OBz	**1c**	23	**2c**	90
4	Bn	OAc	**1c′**	23	**2c**	90
5	Ts	OBz	**1d**	45	**2d**	80
6	Ts	OAc	**1d′**	42	**2d**	82
7	Boc	OBz	**1e**	24	**2e**	*e*

[a] Reaction conditions: A mixture of **1** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and bpy (0.038 mmol) in HOAc (2.0 mL) was stirred at 80 °C; the reaction was monitored by TLC. [b] The products were identified by ^{1}H NMR, IR, MS, and elemental analysis or HRMS. [c] Isolated yield. [d] *Z*/*E* > 97:3 [e] No anticipated product was observed

has been developed in which the acetoxy anion served as the nuleophile and the nitrogen-containing ligands were employed to inhibit the β-hydride elimination reaction.[10] The stoichiometric reactions strongly demonstrated that the nitrogen-containing ligands, like halides, serve to favor β-heteroatom elimination over β-hydride elimination.[10] Also a similar strategy was used in the cycloisomerization of the electron-rich 1,6-enynes.[11] The asymmetric version of this acetoxypalladation-initiated enyne-coupling reaction was achieved while chiral nitrogen-containing ligands were employed.[10] Herein we wish to report the asymmetric construction of α-alkylidene-γ-butyrolactams from palladium(II)-catalyzed intramolecular enyne cyclization of *N*-allylic 2-alkynamides based on the above methodology.

Results and Discussion

We initially examined the reaction of *N*-(*Z*)-(4′-X-2′-butenyl)-2-butynamides (X = leaving group) using the reaction conditions for the corresponding esters[10] (Table 1).

Most of the reactions proceeded smoothly to afford the γ-butyrolactams in high yields with high stereoselectivity with respect to the exocyclic double bonds (*Z*/*E* > 97:3).[12] The variation of leaving groups has little influence on the β-heteroatom elimination reaction, which is similar to the reaction initiated by halopalladation.[12b] Change of the substituents on the nitrogen atom of the *N*-allylic 2-alkynamides influenced the cyclization greatly on the yield of the reaction (Table 1, entries 1−3, and 5). The alkynamides with electron-withdrawing substituents on the nitrogen atom required longer reaction time and gave lower yield than those with electron-donating substituents (Table 1, compare entry 3 with 5, and entry 4 with 6). *N*-Benzyl-substituted amides led to the best results. However, no product could be isolated when *N*-Boc is the substituent (Table 1, entry 7) or there is no substituent on the nitrogen atom of the *N*-allylic 2-alkynamides (Table 1, entry 1).

SCHEME 1

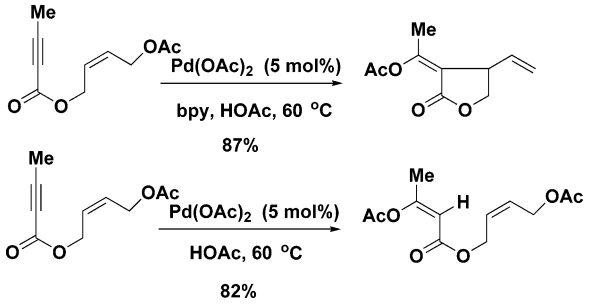
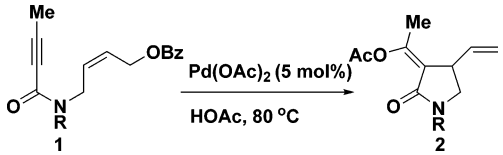


TABLE 2. Cyclization of *N*-(*Z*)-(4′-Benzoyloxybut-2′-enyl)butynamides in the Absence of the Nitrogen Ligands



entry[a]	substrate R		product[b]	yield (%)[c,d]
1	Me	**1b**	**2b**	37
2	Bn	**1c**	**2c**	45
3	Ts	**1d**	**2d**	24

[a] Reaction conditions: A mixture of **1** (0.5 mmol) and $Pd(OAc)_2$ (0.025 mmol) in HOAc (2.0 mL) was stirred at 80 °C and the reaction was monitored by TLC. [b] The products were identified by ^{1}H NMR, IR, MS, and elemental analysis. [c] Isolated yield. [d] *Z*/*E* > 97:3

Further experiments were carried out to study the difference of the cyclization of allylic alkynoates and *N*-allylic alkynamides. As mentioned in the acetoxypalladation-initiated cyclization of allylic butynoates,[10a,b] the cyclization reaction can occur only in the presence of bipyridine as the ligands. When the reaction was carried out in the absence of the nitrogen ligands, only the hydroacetoxylation byproduct was observed (Scheme 1),[10] while in the case of *N*-allylic alkynamides, the cyclization product could be isolated in noticeable yield even in the absence of the nitrogen ligands (Table 2). Combined with the electronic effect of the substituents on nitrogen atom mentioned above, these results revealed that the nitrogen atom of the *N*-allylic alkynamides, to some extent, may also play the role of nitrogen-containing ligand in stabilizing the carbon−palladium bond, inhibiting the β-hydride elimination and promoting the β-heteroatom elimination.[10b,c,13]

Variation of the substituted group R^1 on the alkyne of the *N*-allylic 2-alkynamides influenced the cyclization moderately on the yield of the reaction. However, attempts to cyclize the *N*-(*Z*)-(4′-acetoxy-2′-butenyl)propynamide (**1f**) met with failure, which was in accord with $Pd(OAc)_2$-catalyzed hydroacetoxylation of 2-alkynoates[14] and might be attributed to the possible formation of (alkynyl)palladium species[15] (Table 3, entry 1). When R^1 is methyl, the yield of the enyne-coupling product is the highest (Table 3, entry 2). For larger R^1 groups, the yield is

(10) (a) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (b) Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* **2001**, *66*, 7676. (c) Lu, X.; Zhang, Q. *Pure Appl. Chem.* **2001**, *73*, 247.

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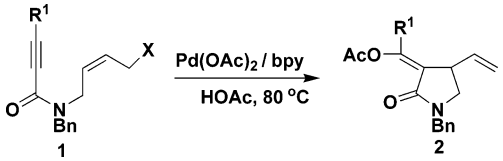
(13) Similar results related to stabilizing the carbon−transition metal bond and inhibiting the β-hydride elimination by coordination have been reported: (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. (b) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723. (c) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387. (d) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186. (e) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

(14) Lu, X.; Zhu, G.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 7205.

TABLE 3. Cyclization of *N*-(*Z*)-(4′-X-2′-butenyl)-2-alkynamides (X = leaving group)



	substrate				
entry[a]	R^1	X		product[b]	yield (%)[c,d]
1	H	OBz	**1f**	**2f**	*e*
2	Me	OBz	**1c**	**2c**	90
3	*n*-Bu	OBz	**1g**	**2g**	71
4	$MeOCH_2$	OBz	**1h**	**2h**	81
5	Ph	OBz	**1i**	**2i**	74
6	Me	OAc	**1c′**	**2c**	90
7	*n*-Bu	OAc	**1g′**	**2g**	77
8	$MeOCH_2$	OAc	**1h′**	**2h**	86
9	Ph	OAc	**1i′**	**2i**	80

[a] Reaction conditions: A mixture of **1** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and bpy (0.038 mmol) in HOAc (2.0 mL) was stirred at 80 °C; the reaction was monitored by TLC. [b] The products were identified by ^1H NMR, IR, MS, and elemental analysis or HRMS. [c] Isolated yield. [d] *Z*/*E* > 97:3. [e] No product was observed.

a little lower (except for Ph). In all cases, the reaction gave high *Z*-selectivity of the exocyclic double bond without the detection of *E*-exocyclic double bonds.[12] In addition, the reaction of *N*-(*E*)-(4′-benzoyloxy-2′-butenyl)-2-butynoamide was ineffective under the same reaction conditions, and the starting material remained intact after 24 h even at elevated temperature (100 °C). This result is similar to the cyclization of enyne esters initiated by acetoxypalladation,[10] but is different from that initiated by halopalladation.[16] The stronger coordinating ability of (*Z*)-olefins compared to (*E*)-olefins may account for the discrepancy.[17]

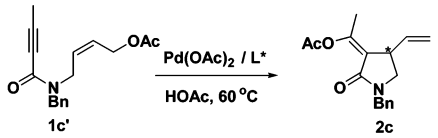
With these results in hand, we made an effort to develop an asymmetric version of this reaction. In the work on the asymmetric cyclization of alkynoates, the employment of pymox-Ph or phenyl-substituted bisoxazoline as the ligands led to the remarkable yield and high enantioselectivity (up to 92% ee).[10] Thus, **1c′** was selected to examine the asymmetric cyclization leading to γ-butyrolactams (Table 4).

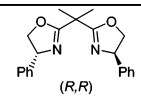
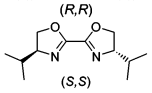
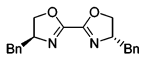
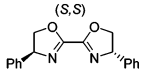
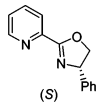
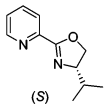
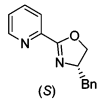
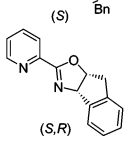
Unfortunately, low enantioselectivity (8−59% ee) was achieved when the substrates were *N*-benzyl-substituted alkynamides. Based on the supposition discussed above that the nitrogen atom of the alkynamide may also coordinate with the palladium atom, there might exist competition between the alkynamides and the chiral nitrogen-containing ligands in coordination with the palladium[18] resulting in a low enantioselectivity. When an alkynamide with an electron-withdrawing group on the nitrogen atom was used as the substrate, the enantioselectivity did increase as shown in Table 5. Finally, a moderate enantioselectivity up to 72% ee was obtained for a tosyl group substituted alkynamide, using pymox-Ph as the ligand.

The results show that not only the substituted groups on the nitrogen atom of alkynamides but also the leaving groups have much influence on the enantioselectivity. Despite using pymox (pyridyl monooxazoline)[19] or bisoxazoline[20] as the chiral ligand, the enantioselectivities of the reaction of *N*-tosylalkynamides are much better than those of the reaction of *N*-benzylalkynamides. The bulky leaving group is led to further enhancement in the enantioselectivity of this reaction. Both the electron-withdrawing group on the nitrogen atom of alkynamides and the bigger leaving group had a positive effect on the asymmetric cyclization of alkynamides initiated by acetoxypalladation. Further experiments showed that if the ratio of ligand and $Pd(OAc)_2$ was increased, not only was the yield enhanced a little, but the enantioselectivity improved as well (Table 6).

The plausible mechanism for this transformation is believed to be analogous to that of the halopalladation-initiated cycliza-

TABLE 4. Asymmetric Cyclization of *N*-Benzyl-*N*-(*Z*)-(4′-acetoxyl-2′-butenyl)-2-butynamide (1c′) with Different Chiral Ligands[a]



entry[a]	L*	time (h)	yield (%)[b,c]	ee (%)[d]
1	 (*R*,*R*)	23	96	35
2	 (*S*,*S*)	29	85	13
3	 (*S*,*S*)	17	82	8
4	 (*S*,*S*)	4	84	24
5	 (*S*)	54	90	59
6	 (*S*)	15	91	12
7	 (*S*)	17	87	15
8	 (*S*,*R*)	14	88	23

[a] Reaction conditions: $Pd(OAc)_2$ (0.025 mmol), substrate (0.5 mmol), L* (0.038 mmol) in HOAc (2 mL) at 60 °C. [b] Isolated yield. [c] *Z*/*E*>97:3. [d] Determined by chiral HPLC, using the chiral AD column eluting with hexane/2-propanol (95/5) (λ = 254 nm).

(15) (a) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698. (b) Melikyan, G. G.; Nicholas, K. M. In *Mordern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: New York, 1995; p 79.

(16) Zhu, G.; Ma, S.; Lu, X. *J. Chem. Res.* (*S*) **1993**, 366.

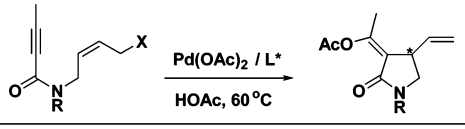
(17) Hartley, F. R. *The Chemistry of Platinum and Palladium*; Applied Science Publishers Ltd: London, UK, 1973; p 377.

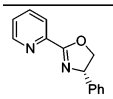
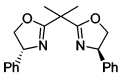
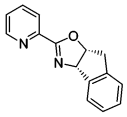
(18) Lee, C.-W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000**, *2*, 1213.

(19) (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. (b) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *J. Org. Chem.* **1997**, *62*, 7937. (c) Cheng, J.; Deming, T. J. *Macromolecules* **1999**, *32*, 4745.

(20) (a) Corey, E. J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.

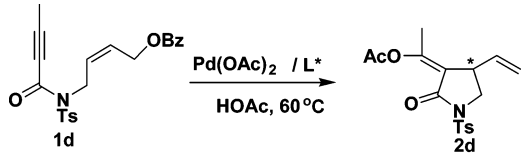
TABLE 5. Asymmetric Cyclization of Alkynamides[a]

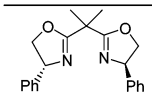


L*	R	X	product	yield (%)[b, c]	ee (%)[d]
	Bn	OBz	**2c**	90	59
	Bn	OAc	**2c**	90	54
(*S*)	Ts	OBz	**2d**	76	72
	Bn	OBz	**2c**	91	49
	Bn	OAc	**2c**	96	35
(*R,R*)	Ts	OBz	**2d**	79	61
	Ts	OAc	**2d**	81	65
	Bn	OBz	**2c**	85	62
	Bn	OAc	**2c**	88	23
(*S,R*)	Ts	OBz	**2d**	72	67
	Ts	OAc	**2d**	82	48

[a] Reaction conditions: Pd $(OAc)_2$ (0.025 mmol), substrate (0.5 mmol), L* (0.038 mmol) in HOAc (2 mL) at 60 °C. [b] Isolated yield. [c] *Z*/*E* > 97:3. [d] Determined by chiral HPLC when R = Bn, using the chiral AD column eluting with hexane/2-propanol (95/5) (λ = 254 nm), when R = Ts, using the chiral AS column eluting with 60:40 hexane:2-propanol (λ = 254 nm).

TABLE 6. Asymmetric Cyclization of 1d[a]



L*	L*/ Pd	yield (%)[b,c]	ee (%)[d]
	1.5	79	61
	3.0	86	80
(*R, R*)			

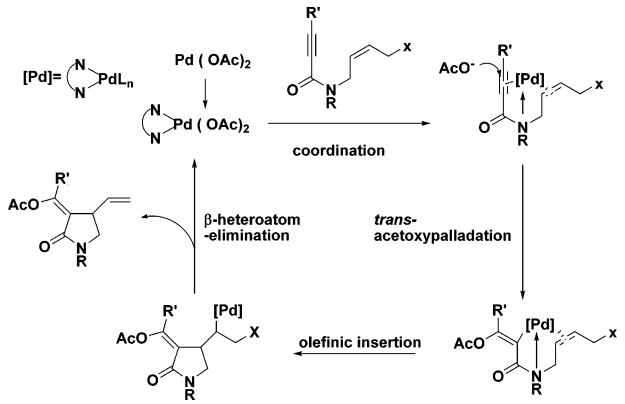
[a] Reaction conditions: $Pd(OAc)_2$ (0.025 mmol), substrate (0.5 mmol), L* in HOAc (2 mL) at 60°C. [b] Isolated yield. [c] *Z*/*E* > 97:3. [d] Determined by chiral HPLC, using the chiral AS column eluting with hexane/2-propanol (60/40) (λ = 254 nm).

tion of enyne amides.[8] This will involve intramolecular insertion of the olefin into the vinyl-palladium intermediate formed by *trans*-acetoxypalladation of the carbon−carbon triple bond, followed by *β*-heteroatom elimination to give the *γ*-butyrolactam and the Pd(II) species making the catalytic cycle possible (Scheme 2).

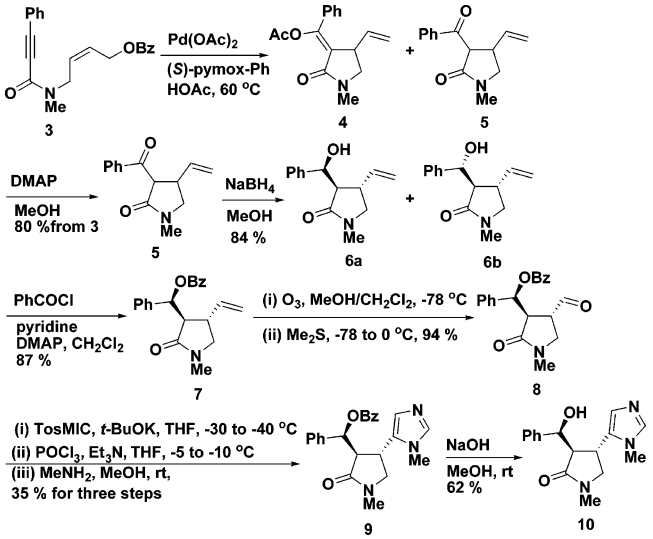
On the basis of these results, we turned our attention to the total synthesis of the natural product, (−)-isocynometrine,[21] to demonstrate the synthetic utility of the asymmetric protocol (Scheme 3). Similar to our reported work of the synthesis of (±)-isocynometrine,[8] *N*-methyl *N*-(*Z*)-(4′-benzoyloxy-2′-butenyl)-3-phenylpropynamide (**3**) was selected as the starting compound. The asymmetric cyclization of **3** with our catalytic system using (*S*)-pymox-Ph as the ligands gave a mixture of **4** and **5**. This implies that the hydrolysis of the vinyl acetate in **4** is much easier than that of the vinyl bromide as reported.[8] After hydrolysis without separation, an 80% yield of **5** was isolated with 53% ee. Reduction of **5** with $NaBH_4$ gave a pair of diastereisomers **6a** and **6b** in a 2.5:1 ratio, which could be separated by column chromatography. Compound **6a** was regarded as the required intermediate in our synthesis according to its spectral data.[8] Protection the hydroxy group of **6a** with the benzoyl group gave **7** (yield 87%, 80.5% ee) and then ozonolysis of the double bond at −78 °C produced the corresponding aldehyde **8**. The aldehyde **8** was treated successively in three steps without purification to construct the imidazole ring to obtain **9** according to the literature[8] and then deprotected to give the target molecule (−)-isocynometrine (**10**), mp 177−179 °C, yield 62% with 98.1% ee ($[\alpha]^{20}_D$ −63.7 (*c* 0.7, $CHCl_3$) [lit.[21] $[\alpha]^{20}_D$ −66 (*c* 1.0, $CHCl_3$)]).

In summary, we developed the synthesis of *γ*-butyrolactams from the cyclization of enyne amides initiated by acetoxypalladation in the presence of nitrogen-containing ligands under

SCHEME 2. The Plausible Mechanism



SCHEME 3. Total Synthesis of (−)-Isocynometrine (10)



(21) (a) Chiaroni, A.; Riche, C.; Tchissambou, L.; Khuong-Huu, F. *J. Chem. Res.* (*S*) **1981**, 182; *J. Chem. Res.* (*M*) **1981**, 2116. (b) Tchissambou, L.; Benechie, M.; Khuong-Huu, F. *Tetrahedron* **1982**, *38*, 2687.

Pd(II) catalysis with high efficiency and stereoselectivity. Employing the nitrogen-containing chiral ligands, the catalytic asymmetric protocol was established with moderate enantioselectivity (up to 80% ee). The nitrogen atom of the *N*-allylic alkynamides might compete with the nitrogen-containing chiral ligands in coordination with palladium, which might be the reason for the low enantioselectivity as compared with that of γ-butyrolactones. The synthetic utility of this asymmetric cyclization was exemplified by the total synthesis of (−)-isocynometrine. Further studies for the asymmetric reaction are in progress.

Experimental Section

Materials. The chiral ligands were prepared by literature methods.[18,19] The amide starting materials were prepared according to the literature procedure.[8] Procedures and data for the starting materials were available in the Supporting Information.

Cyclization of *N*-(*Z*)-(4′-X-2′-butenyl)alk-2-ynamides (X = leaving group): Typical Procedure. To a solution of $Pd(OAc)_2$ (0.025 mmol) and ligand (0.038 mmol) in HOAc (2 mL) was added the substrate (0.5 mmol). The reaction was carried out at 80 (for nonchiral ligands) or 60 °C (for chiral ligands). After the reaction was completed as monitored by TLC, ether was added. The mixture was washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography (300−400 mesh silica gel, petroleum ether/ethyl acetate) to give the cyclization product.

***N*-Methyl-α-(*Z*)-(1′-acetoxyethylidene)-β-vinyl-γ-butyrolactam (2b).** Oil; ^{1}H NMR (300 MHz $CDCl_3$) δ 5.82−5.76 (m, 1H), 5.25−5.13 (m, 2H), 3.63 (m, 2H), 3.06 (dd, $J_1 = 1.6$ Hz, $J_2 = 9.3$ Hz, 1H), 2.84 (s, 3H), 2.25 (s, 3H), 1.92 (s, 3H); MS *m*/*z* 210 ($M^+ + 1$), 168, 167, 140, 124 (100), 98, 96, 44, 43; IR (neat) ν 2920, 1760, 1672, 1639, 1189, 920 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.84; H, 7.58; N, 6.53.

For the data for other starting materials, see the Supporting Information.

The procedure for the asymmetric cyclization of *N*-(*Z*)-(4′-X-2′-butenyl)-2-alkynoamides (**2c** or **2c′**) (X = OBz or OAc) was similar as above. The percent ee values were determined by HPLC, using the chiralcel AD column eluting with hexane:2-propanol (v/v 95/5) ($\lambda = 254$ nm) when R = Bn and the chiralcel AS column eluting with hexane:2-propanol (v/v 60/40) ($\lambda = 254$ nm) when R = Ts.

The synthesis of (−)-isocynometrine was similar to the reported method of the synthesis of (±)-isocynometrine. See the Supporting Information.

10: mp 177−179 °C; yield 62% with 98.1% ee; IR (KBr) ν 3097, 2837, 1687, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29−7.21 (m, 5 H), 7.10 (s, 1 H), 6.69 (s, 1 H), 5.05 (br, 1 H), 4.84 (d, $J = 8.4$ Hz, 1 H), 3.45 (t, $J = 9.6$ Hz, 1 H), 3.24 (dd, $J = 9.6$, 6.3 Hz, 1 H), 3.15−3.08 (m, 1 H), 3.10 (s, 3 H), 2.99 (t, $J = 8.1$ Hz, 1 H), 2.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 139.6, 137.6, 132.4, 128.3, 126.9, 125.9, 75.2, 54.9, 54.8, 30.9, 29.7, 29.6; MS (ESI) *m*/*z* 286 ($M^+ + 1$); $[\alpha]^{20}_D$ −63.7 (*c* 0.7, $CHCl_3$).[21]

Acknowledgment. The authors thank the Major State Basic Research Program (Grant G20000077502-A). We also thank the National Natural Sciences Foundation of China (20072045) and the Chinese Academy of Sciences for the financial support.

Supporting Information Available: Synthetic procedures and data for the starting materials, the cyclization lactams, the asymmetric cyclization products, and the total synthesis of (−)-isocyanometrine. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060288W