Regiocontrolled Iodoaminocyclization Reaction of an Ambident Nucleophile Mediated by Basic Metallic Reagent

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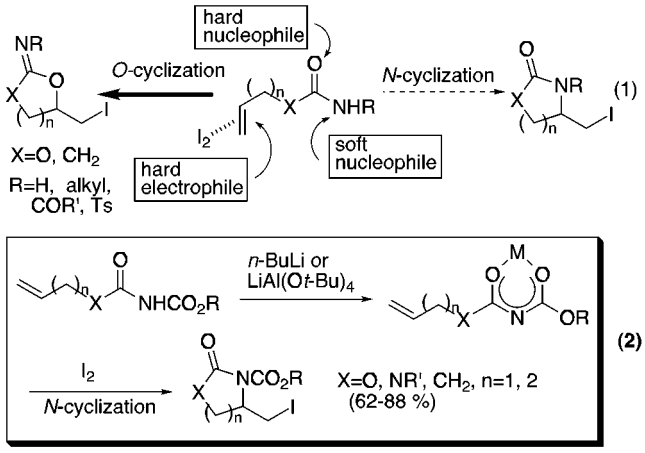
A new and general method of iodine-mediated cyclization reactions of allyl or homoallyl carbamates, ureas, and amides was found to give *N*-cyclized products as single regioisomers. The present reaction proceeded in good yield through regiocontrol (*N*-cyclization > *O*-cyclization) and the increase in the reactivity of an ambident nucleophile by a basic metallic reagent. The *N*-cyclization selectivity was remarkably affected by the additive employed. The iodoaminocyclization reaction of the homoallyl carbamates and ureas with a chiral center at the homoallylic position was found to proceed with high 1,3-*cis*- and 1,3-*trans*-selectivity, respectively.

Introduction

Halocyclization of unsaturated compounds with an intramolecular nucleophilic center plays an important role in the stereoselective construction of cyclic compounds and functionalization of double bonds.[1] In the halocyclization reaction of olefinic compounds having an ambident nucleophile such as carbamate, urea, or amide, *O*-cyclized products are generally obtained in preference to *N*-cyclized products (Scheme 1, eq 1).[2] The *O*-selective cyclization in these reactions can be easily understood on the basis of the HSAB theory; that is, an oxygen atom, more electronegative than a nitrogen atom, should preferentially attack the iodine−olefin π-complex characterized as a hard electrophile.

To obtain *N*-cyclized products in these substrates, the reactions of *N*-tosylcarbamates (X = O, n = 1, 2) and -amides (X = CH_2, n = 0) with lower pK_a values or *N*,*O*-bis(trimethylsilyl) derivatives of 4-alkenamide (n = 1) have been reported.[3,4] However, these methods based on the modification of the substrates are quite limited; for example, in the use of tosyl derivatives, the 5-membered-ring-forming reactions of *N*-tosyl-4-pentenamide (n = 1, X = CH_2) or urea (n = 1, X = NH) give *O*-cyclized products as the major isomers (eq 1).[5] Furthermore, the application of bis-silylation to a 6-membered lactam-forming reaction results in a considerable decrease in chemical yield.[4] Although the preparation of oxazolidinone or lactam derivatives through halocyclization of unsaturated thiocarbimidate or thioimidate has been reported, the yields in iodolactamization of thioimidates are moderate, and there has been no report regarding 6-membered lactam formation.[6]

Scheme 1



In this paper, we report the results of a new and general method for an iodine-mediated cyclization reaction which gives *N*-cyclized products as a single isomer with substrates (X = O, NR′, CH_2, n = 1, 2) shown in eq 2.[7] The present reaction proceeded in good yield through regiocontrol (*N*-cyclization > *O*-cyclization) and an increase in the reactivity of an ambident nucleophile by a basic metallic reagent such as LiAl(O-*t*-Bu)$_4$ or *n*-BuLi.[8] The selectivity of *N*-cyclization was remarkably affected by the additive employed. Furthermore, the iodoaminocyclization reaction of the homoallyl carbamates and ureas with a chiral center at the homoallylic position was found to proceed with high 1,3-*cis*- and 1,3-*trans*-selectivity, respectively.

Results and Discussion

Additive Effect in the Iodocyclization of Unsaturated Substrates with an Ambident Nucleophile.

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

(1) (a) Bouqalt, M. J. *C. R. Hebd, Seances Acad. Sci*. **1904**, *139*, 864. (b) Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orland, FL, 1984; Vol. 3, p 411. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(2) (a) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, *18*, 1625. (b) Hirama, M.; Uei, M. *Tetrahedron Lett*. **1982**, *23*, 5307. (c) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (d) Murata, S.; Suzuki, T. *Chem. Lett*. **1987**, 849. (e) Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett*. **1992**, 33, 1299.

(3) (a) Biloski, A. J.; Wood, R. D.; Ganem B. *J. Am. Chem. Soc.* **1982**, *104*, 3233. (b) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett*. **1984**, 4963.

(4) Knapp, S.; Levorse, A. *J. Org. Chem*. **1988**, *53*, 4006.

(5) See ref 18 in 3a. We also found that the reaction of *N*-tosyl-*N*′-allylurea in the presence of I_2 and $NaHCO_3$ gave a mixture of *O*- and *N*-cyclized products in a ratio of 2:1.

(6) (a) Knapp, S.; Patel, D. V. *J. Am. Chem. Soc*. **1983**, *105*, 6985. (b) Knapp, S.; Patel, D. V. *J. Org. Chem*. **1984**, *49*, 5072. (c) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1987**, *26*, 359. (d) Takahata, H.; Takamatsu, T.; Mozumi, M.; Chen, Y.-S.; Yamazaki, T.; Aoe, K. *J. Chem. Soc., Chem. Commun*. **1987**, 1627.

(7) Preliminary communication of this work: Kitagawa, O.; Fujita, M.; Li, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 615.

(8) As a novel halocyclization mediated by a basic metallic reagent, we have also succeeded in the development of a Ti(OR)$_4$-mediated iodocarbocyclization reaction of alkenylmalonate derivatives and its asymmetric catalysis. Kitagawa, O.; Inoue, T.; Taguchi, T. *Rev. Heteroat. Chem*. **1996**, *15*, 243.

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Scheme 2

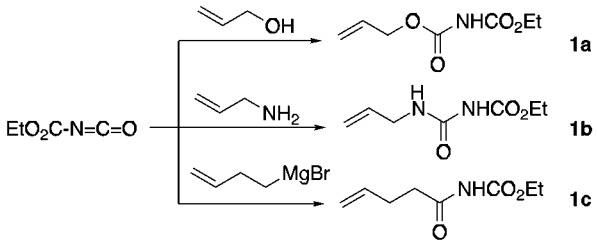
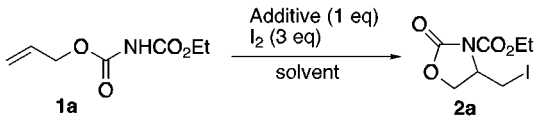


Table 1. Additive Effect in the Iodocyclization of 1a[a]



Entry	Additive	Solvent	Yield (%)[b]
1	none	Et_2O	0
2	NIS (instead of I_2)	Et_2O	0
3	$NaHCO_3$	Et_2O	11
4	$Zr(On\text{-}Bu)_4$	toluene	0
5	$Al(Ot\text{-}Bu)_3$	toluene	29
6	$Ti(Ot\text{-}Bu)_4$	toluene	58
7	NaH	THF	80
8	*n*-BuLi	THF	81
9	$LiAl(Ot\text{-}Bu)_4$	toluene-THF	85

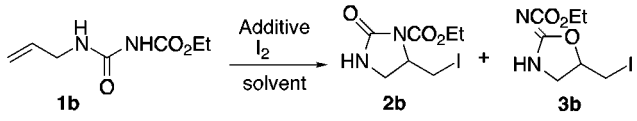
[a] Iodocyclization:**1a** (0.5 mmol), I_2 (1.5 mmol), Additive (0.5mmol), solvent (6 mL), rt, 20-25 h. [b] Isolated yield.

N-Ethoxycarbonylated allyl carbamate **1a**, *N*′-allylurea **1b**, and 4-pentenamide **1c** which can be more easily deprotected than the corresponding *N*-tosyl derivatives were chosen as substrates. These were readily prepared from ethoxycarbonyl isocyanate (commercially available)[9] in accordance with Scheme 2, and the regioselectivities in the iodocyclization were investigated in the presence of various additives (1 equiv) and I_2 (3 equiv).

Under usual conditions (I_2, NIS, or $I_2-NaHCO_3$), the iodocyclization of **1a** did not proceed or gave *N*-cyclized product **2a** in poor yield due to the low nucleophilicity of the nitrogen atom of **1a** (Table 1, Entries 1−3). After a survey of basic reagents for the improvement of nucleophilicity, we found that the reaction of **1a** with a relatively strong base such as NaH, *n*-BuLi, or $LiAl(O\text{-}t\text{-}Bu)_4$ proceeds to give *N*-cyclized product **2a** in good yield without the formation of any *O*-cyclized product (entries 7−9). In this reaction, the use of the *N*-ethoxycarbonyl derivative is required to obtain the *N*-cyclized product; for example, the reaction of unsubstituted allyl carbamate itself did not proceed even in the presence of $LiAl(O\text{-}t\text{-}Bu)_4$, resulting in the recovery of the starting material.

Although the iodocyclization of *N*-(ethoxycarbonyl)-*N*′-allylurea (**1b**) proceeded in good yield under usual conditions ($I_2-NaHCO_3$), in this case, *O*-cyclized product **3b** was obtained as a single regioisomer (Table 2, entry 1). Contrary to this result, the reaction in the presence of *n*-BuLi or $LiAl(O\text{-}t\text{-}Bu)_4$ gave *N*-cyclized product **2b** in good yield with almost complete regioselectivity (entries 6 and 7). Thus, in the reaction of **1b**, a remarkable additive effect on the regioselectivity of the ambident nucleophile was observed. The *N*-selective cyclization by the use of *n*-BuLi or $LiAl(O\text{-}t\text{-}Bu)_4$ is noteworthy; that is, the use of other metallic reagents such as $Ti(O\text{-}t\text{-}Bu)_4$, $Al(O\text{-}t\text{-}Bu)_3$, or even NaH, which gave excellent selectivity in the reaction of **1a**, resulted in a mixture of **2b** and **3b** in a ratio of 1:2−3.5:1 (entries 3−5).

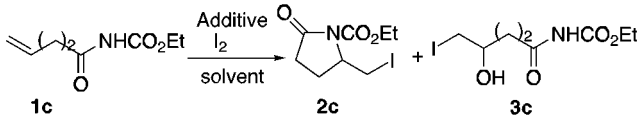
Table 2. Additive Effect in the Iodocyclization of 1b[a]



Entry	Additive	Solvent	Yield **2b**	**3b** (%)[b]
1	$NaHCO_3$	Et_2O	0	77
2	*t*-BuOK	toluene	0	18
3	$Al(Ot\text{-}Bu)_3$	toluene	12	24
4	$Ti(Ot\text{-}Bu)_4$	toluene	54	16
5	NaH	THF	45	21
6	*n*-BuLi	THF	88	trace
7	$LiAl(Ot\text{-}Bu)_4$	toluene-THF	88	0

[a] Iodocyclization:**1a** (0.5 mmol), I_2 (1.5 mmol), Additive (0.5 mmol), solvent (6 mL), rt, 18-36 h. [b] Isolated yield.

Table 3. Additive Effect in the Iodocyclization of 1c[a]



Entry	Additive	Solvent	Yield **2c**	**3c** (%)[b]
1	$NaHCO_3$	Et_2O	0	53
2	NaH	THF	51	14
3	*n*-BuLi	THF	68	trace
4	$LiAl(Ot\text{-}Bu)_4$	toluene-THF	69	0

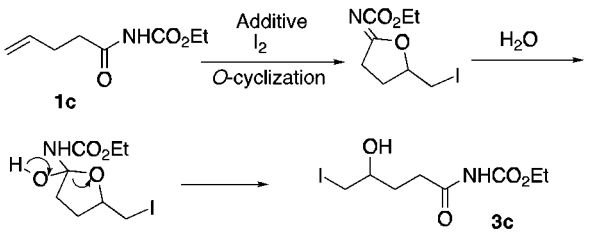
[a] Iodocyclization:**1a** (0.5 mmol), I_2 (1.5 mmol), Additive (0.5 mmol), solvent (6 mL), rt, 18-36 h. [b] Isolated yield.

This additive effect on the regiocontrol of the ambident nucleophile was also found in the reaction of *N*-(ethoxycarbonyl)-4-pentenamide (**1c**) (Table 3). The reaction of **1c** with $NaHCO_3-I_2$ gave iodohydrin **3c** as the sole product without the formation of lactam **2c** (entry 1). The iodohydrin **3c** was formed even under anhydrous conditions using NaH, and in this case, a mixture of **2c** and **3c** was obtained in a ratio of **2c**/**3c** = 3.6 (entry 2). Thus, **3c** may be formed through iodocyclization by *O*-attack of the amide-carbonyl and the subsequent hydrolysis of the imino ether intermediate as shown in Scheme 3,[10] but not by intermolecular addition of I_2 and H_2O to the double bond. Similar to **1b**, the use of *n*-BuLi or $LiAl(O\text{-}t\text{-}Bu)_4$ was the most effective to give *N*-cyclized product **2c** in 68% or 69% yield as a single regioisomer, respectively (entries 3 and 4).

(9) Ethoxycarbonyl isocyanate was purchased from Aldrich Co.

(10) (a) Maligres, P. E.; Upadhyay, V.; Rossen, K.; Cianciosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 2195. (b) Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 6843.

Scheme 3



Although the origin of *N*-cyclization selectivity is not clear, in these reactions, *n*-BuLi or LiAl(O-*t*-Bu)$_4$ may bring about an increase in the reactivity together with regiocontrol of an ambident nucleophile through the formation of a metal imino alkolate intermediate (Scheme 1, eq 2).

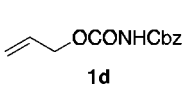
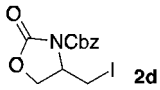
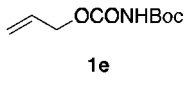
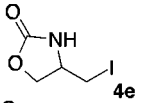
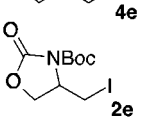
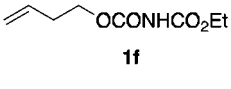
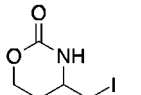
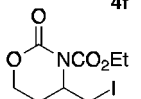
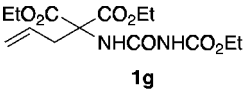
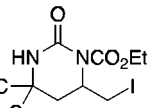
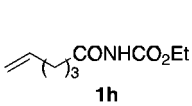
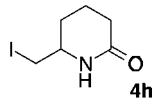
Iodoaminocyclization Reaction with Various Substrates. On the basis of the above reaction conditions, the iodoaminocyclization of various substrates **1d**−**1h** was further examined. Carbamates **1d** and **1e** were prepared according to reported procedures.[11] On the other hand, **1f**, **1g**, and **1h** were prepared by the reaction of ethoxycarbonyl isocyanate with homoallyl alcohol, diethyl α-amino-α-allylmalonate and 4-pentenylmagnesium bromide, respectively (see Scheme 2).

The results of the reactions using LiAl(O-*t*-Bu)$_4$ or *n*-BuLi are shown in Table 4. In the presence of LiAl(O-*t*-Bu)$_4$ and I$_2$, the reaction of *N*-Cbz or *N*-Boc derivatives **1d** and **1e**, which can be easily deprotected in comparison with *N*-ethoxycarbonyl derivative **1a**, also proceeded in good yields to give *N*-cyclized products **2d** and **4e**, respectively, without the formation of any *O*-cyclized product (entries 1 and 2). In the case of **1e**, *N*-unsubstituted cyclic carbamate **4e** was obtained through iodocyclization and subsequent loss of the Boc group (entry 2).

This method can be also applied to the 6-membered ring-forming reaction. Thus, the reaction of homoallyl carbamate **1f**, urea **1g**, and 5-hexenamide **1h** gave *N*-cyclized products **4f**, **2g**, and **4h** as single regioisomers (Entries 4, 6, and 7). In the reaction of **1e**−**1h**, the formation of dealkoxycarbonylated products **4** was depending on the reaction conditions and the structure of products **2** (Entries 2, 4, 6, and 7). For example, prolonged reaction time brought about an increase in such dealkoxycarbonylated products, and generally, 6-membered-ring products were easily dealkoxycarbonylated as compared with 5-membered products **2a**−**2d**. These dealkoxycarbonylated reactions may be caused by LiI and Al(O-*t*-Bu)$_3$ generated after iodoaminocyclization.[12] The best yield in each reaction obtained under optimized conditions at present is shown in Table 4.

The dealkoxycarbonylation was not generally observed in the use of *n*-BuLi as a basic reagent; that is, the reaction of **1e** and **1f**, which led to dealkoxycarbonylated products **4e** and **4f** by using LiAl(O-*t*-Bu)$_4$, gave *N*-ethoxycarbonyl derivative **2e** and **2f** (Entries 3 and 5). However, in the 6-membered ring-forming reaction with amide **1h**, the use of *n*-BuLi resulted in the formation of a complex mixture.

Table 4. Iodoaminocyclization in the Presence of LiAl(O-*t*-Bu)$_4$ or *n*-BuLi[a]

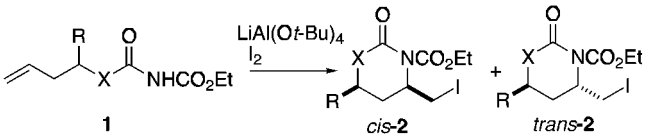
Entry	Substarates	Temp.	Time (h)	Products	Yield (%)[b]
1	 **1d**	rt	24	 **2d**	79
2	 **1e**	rt	24	 **4e**	68
3[c]	**1e**	rt	2	 **2e**	58
4	 **1f**	rt	20	 **4f**	73
5[c]	**1f**	rt	2	 **2f**	73
6	 **1g**	0 °C	20	 **2g**	86[d]
7	 **1h**	0 °C	24	 **4h**	62[e]

[a] Iodocyclization:**1** (0.5 mmol), I$_2$ (1.5 mmol), 1M THF solution of LiAl(O*t*-Bu)$_4$, toluene (6 mL). [b] Isolated yield. [c] In these cases, *n*-BuLi (0.5 mmol) as a basic reagent and THF (6 mL) as a solvent were used. [d] The reaction at rt gave a mixture of **2g** and dealkoxycarbonylated product. [e] In this case, the reaction in THF gave a higher yield than that in toluene.

Diasteroselective Iodoaminocyclization of Homoallyl Carbamates and Ureas with a Chiral Center at the Homoallylic Position. It has been reported that iodocyclization of *O*-homoallyl or *N*-homoallyl carbamate with a chiral center at the homoallylic position proceeds with high 1,3-*cis*-selectivity or 1,3-*trans*-selectivity, respectively, through six-membered chair-like transition states.[2b,13] In comparison with high 1,3-asymmetric inductions in these *O*-cyclizations, the iodoaminocyclization reaction of homoallyl sulfonylcarbamate was reported to proceed with lower diastereoselectivity.[3b] We investigated 1,3-asymmetric induction in the iodoaminocyclization of *O*-homoallyl carbamates **1i** and **1j** or ureas **1k**−**1n** with a chiral center at the homoallylic position under our present reaction conditions.[14] Carbamates **1i** and **1j** were synthesized from 4-penten-2-ol and 1-phenyl-5-hexen-3-ol, respectively (see Scheme 2). Similarly, ureas **1k**−**1n** were also synthesized from 3-amino-1-phenyl-5-hexene, 3-(benzylamino)-1-phenyl-5-hexene, 3-(diphenylmethylamino)-1-phenyl-5-hexene, and 2-(diphenylmethylamino)-4-pentene, respectively. These unsaturated amines were prepared according to reported procedures.[15]

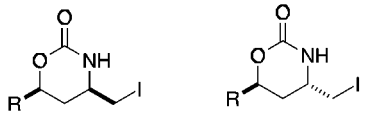
(11) Grehn, L.; Almeida, L. S.; Ragnarsson, U. *Synthesis* **1988**, 993.
(12) In toluene, the treatment of **2f** with LiI (1 equiv) and Al(O-*t*-Bu)$_3$ (1 equiv) gave deethoxycarbonylated product **4f** in 20%, while in the presence of only LiI or Al(O-*t*-Bu)$_3$, the reaction hardly proceeded resulting in the recovery of **2f**.
(13) Ohno, M.; Wang, Y.; Izawa, T.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 6465
(14) Although we also investigated 1,2-asymmetric induction in the reaction of an *O*-allyl carbamate or urea with a chiral center at the allylic position, high stereoselectivity could not be achieved.
(15) Wang, D.; Dai, L.; Hou, X.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187.

Table 5 Diastereoselective Iodoaminocyclization of Homoallyl Carbamates or Ureas with a Chiral Center at Homoallylic Position[a]



Entry	1	X	R	2 Yield (%)[b]		*cis/trans*[c]
1	**1i**	O	Me	**2i**	86	22
2[d]	**1j**	O	$Ph(CH_2)_2$	**2j**	74	50
3	**1k**	NH	$Ph(CH_2)_2$	**2k**	80	2
4	**1l**	$PhCH_2N$	$Ph(CH_2)_2$	**2l**	64	1/30
5	**1m**	Ph_2CHN	$Ph(CH_2)_2$	**2m**	70	≥1/100
6	**1n**	Ph_2CHN	Me	**2n**	64	1/64

[a] Iodoaminocyclization: **1** (0.5 mmol), I_2 (1.5 mmol), $LiAl(Ot\text{-}Bu)_4$ (0.5 mmol), toluene-THF (5 mL-0.5 mL), 0 °C. [b] Isolated yield. [c] The ratio was determined by 300 MHz ^{1}H-NMR. [d] Dealkoxycarbonylated product **4j** was also obtained in 15 % yield (*cis/trans* = 1.7).



R = Me	*cis*-**4i**	*trans*-**4i**
R = $Ph(CH_2)_2$	*cis*-**4j**	*trans*-**4j**

In the presence of $LiAl(O\text{-}t\text{-}Bu)_4$ (1 equiv) and I_2 (3 equiv), the iodocyclization reaction of homoallyl carbamate (**1i**) with a methyl group at the homoallylic position proceeded with high 1,3-*cis*-selectivity (*cis/trans* = 22) to give *N*-cyclized product **2i** in good yield (86%, Table 5, entry 1). In the reaction of **1j** with a phenethyl group, product **2j** was obtained with higher *cis*-selectivity (*cis/trans* = 50) in good yield (74%) together with the formation of dealkoxycarbonylated product **4j** (15%) with a low diastereomer ratio (*cis/trans* = 1.7, entry 2).[16] The low diastereomeric ratio of **4j** may be caused by the preferential dealkoxycarbonylation of *trans*-**2j** in comparison with that of *cis*-**2j**. Thus, the excellent diastereoselectivity observed in the product **2j** may be achieved through a kinetic resolution process on the basis of the preferential dealkoxycarbonylation of *trans*-isomer.

In contrast to the high diastereoselectivity in the iodoaminocyclization of carbametes **1j**, the reaction of homoallylurea **1k** with a phenethyl group at the homoallylic position proceeded with poor *cis*-selectivity (*cis/trans* = 2) to give *N*-cyclized product **2k** (entry 3). In the iodocyclization (*O*-cyclization) of homoallylcarbamate, it has been pointed out that the introduction of a substituent on the nitrogen atom leads to a remarkable increase of the 1,3-*trans*-selectivity.[13] Therefore, the diastereoselectivity of *N*-substituted-*N*-homoallylurea was further examined. As expected, the iodoaminocyclization reaction of **1l** with a benzyl group on the nitrogen atom proceeded with high 1,3-*trans*-selectivity (*cis/trans* = 1/30, entry 4). Furthermore, almost complete *trans*-selectivity was achieved by the introduction of a diphenylmethyl group; that is, the reaction of **1m** gave *trans*-**2m** as a single stereoisomer (entry 5). Similar to **1m**, the reaction of **1n** having a methyl group at the homoallylic position also proceeded with excellent diastereoselectivity (*trans/cis* = 64) by the introduction of diphenylmethyl group to give *trans*-**2m** as a major stereoisomer (entry 6).

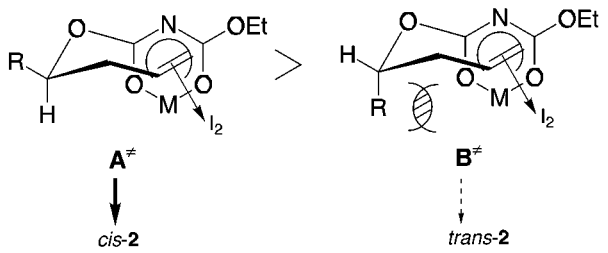


Figure 1. Transition state model of iodoaminocyclization of **1i** and **1j**.

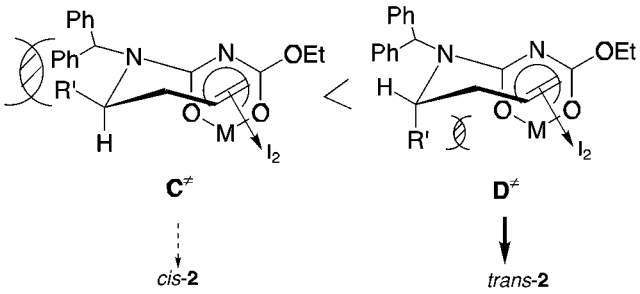


Figure 2. Transition state model of iodoaminocyclization of **1m** and **1n**.

The relative configurations of products **2i**−**2n** were determined on the basis of coupling constants in ^{1}H NMR spectra and NOE experiments (see Supporting Information).

The high 1,3-*cis*-selectivities in the reactions of carbamates **1i** and **1j** can be rationally explained on the basis of the 6-membered chair-like transition state model having an olefinic moiety of equatorial orientation (Figure 1).[17] In the two possible transition state models $A^‡$ and $B^‡$, $A^‡$ with an equatorial alkyl group (R) at homoallylic position should be more favorable than $B^‡$ with an axial group to avoid 1,3-diaxial repulsion between the alkyl group (R) and the iminoalkoxyl part. Thus, the reaction likely proceeds in highly 1,3-*cis*-selective manner through the transition state $A^‡$.

On the other hand, the high *trans*-selectivities observed in the reactions of ureas **1l**−**1n** with benzyl or diphenymethyl groups on the nitrogen atom are in remarkable contrast to the high *cis*-selectivity in the reaction of the corresponding carbamates. These results are possibly explained by the transition state models in Figure 2. In the chair-like transition state models $C^‡$ and $D^‡$ having an olefinic moiety of equatorial orientation,[17] $C^‡$ with an equatorial substituent at the homoallylic position may bring about a steric repulsion between the substituent on the nitrogen atom and the homoallylic substituent. This steric repulsion is anticipated to be stronger than the 1,3-diaxial repulsion between the homoallylic substituent and the iminoalkoxy moeity in transition state model $D^‡$. Thus, the reaction may proceed through the

(16) The use of *n*-BuLi gave **2j** with similar high *cis*-selectivity without formation of dealkoxycarbonylated product **4j** (70%, *cis*-**2j**/*trans*-**2j** = 24).

(17) (a) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533. (b) Labelle, M.; Guindon, Y.; *J. Am. Chem. Soc.* **1989**, *111*, 2204.

transition state model $D^{\ddagger}$ with an axial homoallylic substituent to give *trans*-*N*-cyclized product with a high diastereoselectivity. The low *cis*-selectivity observed in the reaction of *N*-unsubstitued urea **1k** may support the above-mentioned contribution of a steric repulsion between the substituent on the nitrogen atom and the equatorial homoallylic substituent (transition state $C^{\ddagger}$ in Figure 2).

In conclusion, we have succeeded in the development of a new and general method for the iodoaminocyclization reaction of unsaturated carbamates, ureas, and carboxamides through regiocontrol of these ambident nucleophiles by *n*-BuLi or LiAl(O-*t*-Bu)$_4$. Furthermore, the iodoaminocyclization reaction of the homoallyl carbamates and ureas with a chiral center at the homoallylic position was found to proceed with high 1,3-*cis*- and 1,3-*trans*-selectivity, respectively. The present reaction should be widely applicable as a new synthetic method for amino alcohol, diamine, and lactam derivatives.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400- and 300-MHz spectrometers. In the ^{1}H and ^{13}C NMR spectra, chemical shifts are expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact or chemical ionization. Column chromatography was performed on silica gel, Wakogel C-200 (75−150 μm). Preparative TLC was performed on precoated plates (1 mm thickness, 20 × 20 cm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm i.d. prepacked column (silica gel, 50 μm) with a UV detector.

General Procedure for Iodoaminocyclization Reactions with LiAl(O-*t*-Bu)$_4$. A 1 M THF soution of LiAl(O-*t*-Bu)$_4$ (0.5 mL, 0.5 mmol), which was prepared from $LiAlH_4$ and *t*-BuOH (4 equiv) in THF, was added to a solution of **1a** (87 mg, 0.5 mmol) in toluene (6 mL) under an argon atmosphere at rt. After the mixture was stirred for 30 min, I_2 (381 mg, 1.5 mmol) was added, and then the reaction mixture was stirred for 24 h at rt. The mixture was poured into an aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 5:1) gave **2a** (127 mg, 85%).

General Procedure for Iodoaminocyclization Reactions with *n*-BuLi. A 1.36 M hexane solution of *n*-BuLi (0.29 mL, 0.4 mmol) was added to a solution of **1a** (69 mg, 0.4 mmol) in THF (6 mL) under an argon atmosphere at 0 °C. After the mixture was stirred for 30 min, I_2 (305 mg, 1.2 mmol) was added, and then the reaction mixture was stirred for 24 h at rt. The mixture was poured into water and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 5:1) gave **2a** (96 mg, 80%).

3-(Ethoxycarbonyl)-4-(iodomethyl)-2-oxazolidinone (2a). 2a: colorless oil; IR (neat) 2982, 1810, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.32−4.47 (4H, m), 4.19 (1H, m), 3.52 (1H, m), 3.44 (1H, m), 1.38 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 151.1, 150.4, 67.2, 63.6, 54.5, 14.1, 6.8; MS (*m*/*z*) 299 (M^+), 255, 227. Anal. Calcd for $C_7H_{10}INO_4$: C, 28.11; H, 3.37; N, 4.68. Found: C, 28.16; H, 3.57; N, 4.71.

1-(Ethoxycarbonyl)-5-(iodomethyl)-2-imidazolidinone (2b). 2b was prepared from **1b** (86 mg, 0.5 mmol) in accordance with general procedure with LiAl(O-*t*-Bu)$_4$. Purification of the residue by column chromatography (hexane/AcOEt = 1:1) gave **2b** (131 mg, 88%). **2b**: white solid; mp 158−160 °C; IR (KBr) 3259, 1720, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.26 (1H, brs), 4.25−4.42 (3H, m), 3.62 (1H, dd, J = 9.1, 9.3 Hz), 3.50 (1H, dd, J = 2.7, 9.9 Hz), 3.39 (1H, dd, J = 8.8, 9.9 Hz), 3.31 (1H, ddd, J = 1.1, 3.2, 9.8 Hz), 1.35 (1H, t, J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 155.6, 151.5, 62.8, 55.0, 43.2, 14.3, 8.0; MS (*m*/*z*) 298 (M^+), 270, 254; high-resolution MS calcd for $C_7H_{11}IN_2O_3$ 297.9814, found 297.9805. Anal. Calcd for $C_7H_{11}IN_2O_3$: C, 28.21; H, 3.72; N, 9.39. Found: C, 28.15; H, 3.88; N, 9.09.

***N*-(Ethoxycarbonyl)-5-(iodomethyl)oxazolidine-2-imine (3b).** To a solution of **1b** (52 mg, 0.3 mmol) in a mixture of Et_2O (4 mL) and 5% aqueous $NaHCO_3$ (2 mL) was added I_2 (152 mg, 0.6 mmol), and then the mixture was stirred for 18 h at rt. The mixture was poured into an aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 1:1) gave **3b** (69 mg, 77%). **3b**: white solid; mp 101−103 °C; IR (KBr) 3367, 2977, 1655, 1631 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.38 (1H, brs), 4.84 (1H, m), 4.14 (2H, q, J = 7.1 Hz), 3.98 (1H, t, J = 8.7 Hz), 3.62 (1H, dd, J = 6.4, 9.8 Hz), 3.45 (1H, dd, J = 3.9, 10.3 Hz), 3.30 (1H, dd, J = 8.7, 10.3 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 164.1, 76.1, 61.5, 48.3, 14.3, 4.9; MS (*m*/*z*) 298 (M^+), 254, 226; high-resolution MS calcd for $C_7H_{11}IN_2O_3$ 297.9814, found 297.9816.

1-(Ethoxycarbonyl)-5-(iodomethyl)-2-pyrrolidinone (2c). 2c was prepared from **1c** (86 mg, 0.5 mmol) in accordance with the general procedure with LiAl(O-*t*-Bu)$_4$. Purification of the residue by column chromatography (hexane/AcOEt = 5:1) gave **2c** (102 mg, 69%). **2c**: white solid; mp 41−42 °C; IR (KBr) 2981, 1790, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.21−4.45 (3H, m), 3.50 (1H, dd, J = 3.1, 10.0 Hz), 3.45 (1H, dd, J = 7.3, 10.0 Hz), 2.74 (1H, td, J = 9.9, 18.1 Hz), 2.48 (1H, ddd, J = 3.6, 10.2, 18.1 Hz), 2.24 (1H, m), 2.00 (1H, m), 1.36 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 173.2, 151.2, 62.9, 57.5, 31.0, 23.2, 14.1, 9.4; MS (*m*/*z*) 297 (M^+), 156, 84. Anal. Calcd for $C_8H_{12}INO_3$: C, 32.30; H, 4.10; N, 4.70. Found: C, 32.66; H, 4.13; N, 4.71.

***N*-(Ethoxycarbonyl)-4-hydroxy-5-iodopentamide (3c). 3c** was prepared from **1c** (72 mg, 0.4 mmol) in accordance with a procedure similar to that for **3b**. Purification of the residue by column chromatography (hexane/AcOEt = 1:1) gave **3c** (83 mg, 53%). **3c**: white solid; mp 78 °C; IR (KBr) 3441, 3265, 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, brs), 4.22 (2H, q, J = 7.1 Hz), 3.64 (1H, m), 3.36 (1H, dd, J = 4.2, 10.2 Hz), 3.26 (1H, dd, J = 6.5, 10.2 Hz), 2.95 (2H, t, J = 7.1 Hz), 2.57 (1H, d, J = 5.4 Hz), 2.01 (1H, dtd, J = 3.6, 7.2, 14.3 Hz), 1.87 (1H, m), 1.30 (1H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 174.7, 151.8, 70.3, 62.4, 32.5, 30.7, 15.0, 14.2; MS (*m*/*z*) 316 (M^+ + 1), 298, 227, 188. Anal. Calcd for $C_8H_{14}INO_4$: C, 30.49; H, 4.48; N, 4.45. Found: C, 30.87; H, 4.52; N, 4.31.

4-(Iodomethyl)tetrahydro-1,3-oxazin-2-one (4f). 4f was prepared from **1f** (75 mg, 0.4 mmol) in accordance with the general procedure with LiAl(O-*t*-Bu)$_4$. Purification of the residue by column chromatography (hexane/AcOEt = 1:1) gave **4f** (70 mg, 73%). **4f**: white solid; mp 85−87 °C; IR (KBr) 3192, 2977, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.65 (1H, brs), 4.32 (1H, td, J = 4.7, 11.5 Hz), 4.25 (1H, dt, J = 3.0, 11.3 Hz), 3.62 (1H, quint, J = 6.0 Hz), 3.23 (1H, dd, J = 5.7, 10.3 Hz), 3.20 (1H, dd, J = 6.9, 10.3 Hz), 2.17 (1H, m), 1.85 (1H, dddd, J = 4.2, 4.2, 8.6, 18.1 Hz); ^{13}C NMR ($CDCl_3$) δ 154.4, 64.8, 51.1, 27.4, 9.4; MS (*m*/*z*) 241 (M^+), 196, 141, 100. Anal. Calcd for $C_5H_8INO_2$: C, 24.92; H, 3.35; N, 5.81. Found: C, 25.21; H, 3.49; N, 5.75.

1-(Ethoxycarbonyl)-6-(iodomethyl)tetrahydro-1,3-oxazin-2-one (2f). 2f was prepared from **1f** (94 mg, 0.5 mmol) in accordance with the general procedure with *n*-BuLi. Purification of the residue by column chromatography (hexane/AcOEt = 4−2:1) gave **2f** (114 mg, 73%). **2f**: white solid; mp 75−77 °C; IR (KBr) 2982, 1742, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.16−4.41 (5H, m), 3.50 (1H, dd, J = 3.0, 9.9 Hz), 3.33 (1H, dd, J = 9.2, 9.9 Hz), 2.38 (1H, m), 2.22 (1H, m), 1.35 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 153.4, 149.4, 64.2, 63.9, 54.2, 27.9, 14.1, 8.0; MS (*m*/*z*) 313 (M^+), 186. Anal. Calcd for $C_8H_{12}INO_4$: C, 30.69; H, 3.86; N, 4.47. Found: C, 30.98; H, 4.02; N, 4.16.

(4*R,6*R**)-3-(Ethoxycarbonyl)-4-(iodomethyl)-6-methyltetrahydro-1,3-oxazin-2-one (*cis*-2i).** In accordance with the general procedure with LiAl(O-*t*-Bu)$_4$, the reaction mixture of **1i** (101 mg, 0.5 mmol) was stirred for 15 h at 0 °C. Purification of the residue by column chromatography (hexane/

AcOEt = 3:1) gave a mixture of *cis*-**2i** and *trans*-**2i** (*cis*/*trans* = 22:1, 141 mg, 86%). *cis*-**2i**: colorless oil; IR (neat) 2981, 1790, 1757, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.15−4.43 (4H, m), 3.50 (1H, dd, J = 2.7, 9.8 Hz), 3.39 (1H, dd, J = 7.9, 9.8 Hz), 2.49 (1H, ddd, J = 2.0, 8.8, 14.1 Hz), 1.77 (1H, ddd, J = 9.4, 11.8, 14.1 Hz), 1.41 (1H, d, J = 6.3 Hz), 1.35 (3H, t, J = 7.1 Hz) ; ^{13}C-NMR ($CDCl_3$) δ 153.5, 150.2, 72.5, 63.8, 53.8, 37.1, 19.6, 14.1, 10.9; MS (*m*/*z*) 327 (M^+), 242, 200; high-resolution MS calcd for $C_9H_{14}INO_4$ 326.9968, found 326.9965.

(4*R,6*R**)- and (4*R**,6*S**)-1-(Ethoxycarbonyl)-6-(iodomethyl)-4-(2′-phenylethyl)tetrahydro-2-pyrimidone (*cis*-2k and *trans*-2k).** In accordance with the general procedure with LiAl(O-*t*-Bu)$_4$, the reaction mixture of **1k** (145 mg, 0.5 mmol) was stirred for 24 h at 0 °C. Purification of the residue by column chromatography (hexane/AcOEt = 2:1) and then MPLC (hexane/AcOEt = 1:1) gave *cis*-**2k** (less polar, 111 mg, 53%) and *trans*-**2k** (more polar, 55 mg, 27%). *cis*-**2k**: white solid; mp 103−105 °C; IR (KBr) 3217, 2925, 1768, 1703 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.16−7.36 (5H, m), 6.08 (1H, brs), 4.13−4.32 (3H, m), 3.53 (1H, dd, J = 2.9, 9.6 Hz), 3.38 (1H, dd, J = 8.5, 9.6 Hz), 3.32 (1H, m), 2.72 (2H, t, J = 7.8 Hz), 2.45 (1H, ddd, J = 3.3, 8.1, 13.4 Hz), 1.82−1.93 (2H, m), 1.71 (1H, ddd, J = 8.7, 10.4, 13.4 Hz), 1.30 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 154.0, 153.8, 140.4, 128.5, 128.3, 126.2, 63.0, 54.3, 48.4, 37.0, 35.7, 31.6, 14.2, 10.9; MS (*m*/*z*) 416 (M^+), 311, 156; high-resolution MS calcd for $C_{16}H_{21}IN_2O_3$ 416.0597, found 416.0600. *trans*-**2k**: white solid; mp 109−110.5 °C; IR (KBr) 3238, 2931, 1723, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16−7.35 (5H, m), 5.44 (1H, brs), 4.56 (1H, m), 4.30 (2H, dq, J = 2.5, 7.1 Hz), 3.39−3.51 (2H, m), 3.12 (1H, dd, J = 9.9, 11.5 Hz), 2.70 (2H, t, J = 7.8 Hz), 2.59 (1H, ddd, J = 2.0, 4.5, 14.1 Hz), 1.85 (2H, dt, J = 7.0, 7.8 Hz), 1.73 (1H, ddd, J = 4.2, 13.2, 14.1 Hz), 1.33 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 153.7, 151.3, 140.5, 128.5, 128.3, 126.2, 63.3, 53.8, 46.6, 37.8, 31.3, 29.6, 14.2, 3.5; MS (*m*/*z*) 416(M^+), 311, 156. Anal. Calcd for $C_{16}H_{21}IN_2O_3$: C, 46.17; H, 5.08; N, 6.73. Found: C, 46.07; H, 5.06; N, 6.60.

(4*R,6*S**)-1-(Ethoxycarbonyl)-3-(diphenylmethyl)-6-(iodomethyl)-4-(2′-phenylethyl)tetrahydro-2-pyrimidone (*trans*-2m).** In accordance with the general procedure with LiAl(O-*t*-Bu)$_4$, the reaction mixture of **1m** (274 mg, 0.6 mmol) was stirred for 20 h at 0 °C. Purification of the residue by column chromatography (hexane/AcOEt = 5−3) gave *trans*-**2m** (244 mg, 70%). *trans*-**2m**: white solid; IR (neat) 2959, 1749, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12−7.49 (13H, m), 6.85 (2H, d, J = 1.9 Hz), 6.82 (2H, s), 4.24−4.34 (2H, m), 4.18 (1H, tdd, J = 2.4, 5.9, 7.9 Hz), 3.53 (1H, dd, J = 2.3, 9.7 Hz), 3.42 (1H, dd, J = 7.8, 9.7 Hz), 3.37 (1H, m) 2.33−2.48 (2H, m), 2.17 (1H, ddd, J = 7.5, 9.1, 13.8 Hz), 1.89 (1H, ddd, J = 4.7, 10.2, 13.8 Hz) 1.62−1.79 (1H, m), 1.37−1.48 (1H, m), 1.33 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 154.2, 151.5, 139.8, 138.1, 138.0, 129.6, 128.3, 128.2, 128.0, 127.9, 127.7, 127.4, 126.0, 63.0, 62.8, 52.5, 50.7, 33.4, 33.1, 32.6, 14.2, 11.6; MS (*m*/*z*) 582 (M^+), 456, 311, 167, 91; high-resolution MS calcd for $C_{29}H_{31}IN_2O_3$ 582.1379, found 582.1384.

Supporting Information Available: Charactarization data and experimental procedure of **2d**, **2e**, **2g**, **4e**, **4h**, *cis*-**4i**, *trans*-**4i**, *cis*-**2j**, *cis*-**4j**, *trans*-**4j**, *trans*-**2n**, *cis*-**2n**, and *trans*-**5m** and scheme for the determination of relative configurations of **2i**−**2n** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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