t-BuOK-Mediated Iodoaziridination Reaction of *N*-Allylic Tosylamide Derivatives

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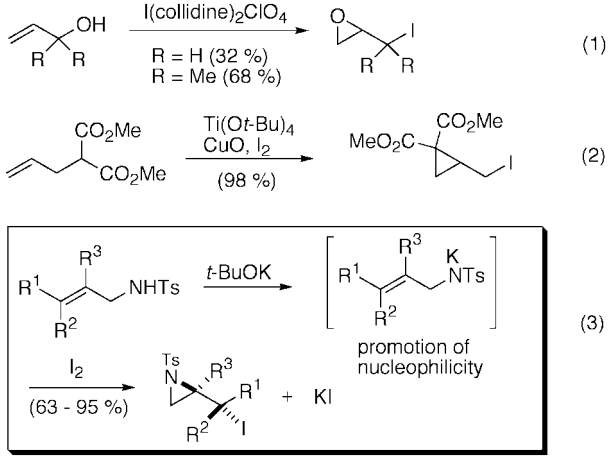
Introduction

In contrast to the preparation of five- or six-membered heterocyclic compounds through halocyclization reactions, a limited number of examples of three-membered heterocyclic-forming reactions have appeared.[1] The reaction of an oxygen nucleophile such as haloepoxidation with allyl alcohol derivatives has been reported, but the chemical yields are generally not satisfactory or not described in detail in the literature (Scheme 1, eq 1).[2,3] In addition, as far as we know, a three-membered ring-forming reaction via the attack of a nitrogen atom as an intramolecular nucleophile has not been reported.

On the other hand, it is well-known that in an intramolecular substitution reaction by a carbanion, a three-membered ring-forming reaction is a more favorable process even in comparison with that for a five- or six-membered ring.[4] In addition, in the course of our work on iodocarbocyclization reactions of alkenylmalonate,[5] we found that a three-membered ring-forming reaction with allylmalonate derivatives proceeds in the presence of I_2, $Ti(OR)_4$, and CuO or pyridine to give (iodomethyl)cyclopropane derivatives in good yields (Scheme 1, eq 2).[6,7] These results prompted us to examine the preparation of three-membered heterocyclic compounds through a halocyclization reaction.

Previously, we reported the result of an iodoaziridination reaction of *N*-allylic tosylamide derivatives that proceeds in a highly stereospecific manner in the presence of a base such as NaH.[8] Under these conditions,

Scheme 1



the reaction of allyl, methallyl, or crotyl derivatives proceeded in good yields, while the reaction of tosylamides having a prenyl group or a cyclic olefin gave a complex mixture or the iodoaziridine in poor yield. In this paper, we report a *t*-BuOK-mediated iodoaziridination reaction that proceeds with complete regioselectivity and stereospecificity (3-*exo*-cyclization and *trans*-addition manner) and can be widely applied to various *N*-allylic tosylamide derivatives (Scheme 1, eq 3). The present reaction provides a stereoselective synthesis of iodoaziridines with two consecutive chiral centers from simple *N*-allylic amides.[9,10]

Results and Discussion

Survey of Reaction Conditions in Iodoaziridination Reaction. The reaction of *N*-allylic tosylamide **1a** with I_2, NIS, or NBS provided an addition product of I_2 to olefin or resulted in the recovery of **1a** because of the low nucleophilicity of tosylamide. To activate the tosylamide, a survey of various basic metallic reagents was performed (Table 1). When $Ti(Oi\text{-}Pr)_4$[5] or $LiAl(Ot\text{-}Bu)_4$[11] was used as a base, no iodoaziridine **2a** was obtained (entries 1, 2). When *n*-BuLi (1 equiv) was used, a considerable solvent effect was observed; that is, in THF the reaction gave an iodination product at the ortho position of the sulfonyl group (17% yield) without formation of the aziridine **2a** (entry 3), while in Et_2O **2a** was obtained in 53% yield (entry 4). In the present reaction,

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(1) (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 411. (b) Gardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (c) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 363.

(2) Examples of haloepoxidation reactions of allyl alcohol derivatives which proceed via an ionic mechanism: (a) Winstein, S.; Goodman, L. *J. Am. Chem. Soc.* **1954**, *76*, 4368. (b) Ganem, B. *J. Am. Chem. Soc.* **1976**, *98*, 858. (c) Midland, M. M.; Halterman, R. *J. Org. Chem.* **1981**, *46*, 1227. (d) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862.

(3) Haloepoxide-forming reaction from allyl alcohol derivatives under radical conditions has been also reported; see: (a) Suginome, H.; Wang, J. B. *J. Chem. Soc., Chem. Commun.* **1990**, 1629. (b) Galatsis, P.; Millan, S. D.; *Tetrahedron Lett.* **1991**, *32*, 7493. (c) Rawal, V. H.; Iwasa, S. *Tetrahedron Lett.* **1992**, *33*, 4687.

(4) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67.

(5) Our reviews in relation to $Ti(OR)_4$-mediated iodocarbocyclization reaction of alkenylmalonates: (a) Taguchi, T.; Kitagawa, O.; Inoue, T. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 770. (b) Kitagawa, O.; Inoue, T.; Taguchi, T. *Rev. Heteroat. Chem.* **1996**, *15*, 243.

(6) (a) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 2167. (b) Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 691.

(7) Beckwith *et al.* also reported an iodocarbocyclization reaction of allylmalonate derivatives which proceeds in the presence of I_2 and NaH: Beckwith, A. L.; Zozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975.

(8) Preliminary communication of this work: Kitagawa, O.; Suzuki, T.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 8371.

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(10) Preparation of halomethylaziridines by other methods and their utilization: (a) Gensler, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 1843. (b) Gensler, W. J.; Brooks, B. A. *J. Org. Chem.* **1966**, *31*, 568. (c) Kimpe, N. D.; Smaele, D. D.; Sakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448 and references cited therein.

(11) Our work in relation to the regiocontrolled iodoaminocylization of unsaturated amide derivatives mediated by $LiAl(Ot\text{-}Bu)_4$: (a) Kitagawa, O.; Fujita, M.; Li, F.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 615. (b) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330.

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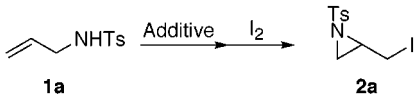
Table 1. Effect of Base in the Iodocyclization of 1a[a]

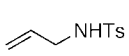
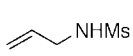
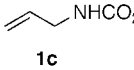
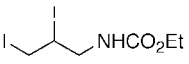
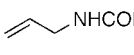
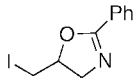


1a **2a**

Entry	Base	Solvent	**2a** Yield (%)[b]
1	Ti(O*i*-Pr)$_4$	toluene	0
2	LiAl(O*t*-Bu)$_4$	toluene	0
3	*n*-BuLi	THF	0
4	*n*-BuLi	Et_2O	53
5	NaH	Et_2O	81
6	*t*-BuOK	toluene	94

[a] Iodocyclization: **1a** (1 mmol), additive (1.5 mmol), I_2 (3 mmol), solvent (5 mL), rt, 15 min−1 h. [b] Isolated yield.

Table 2. *t*-BuOK-Mediated Iodocyclization of Various *N*-Allylic Amides[a]

Entry	Amide **1**	Major product	Yield (%)[b]
1	 **1a**	 **2a**	94
2	 **1b**	 **2b**	45
3	 **1c**		42
4	 **1d**	 **3d**	90

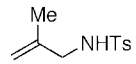
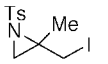
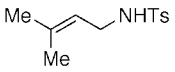
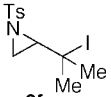
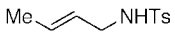
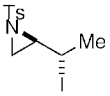
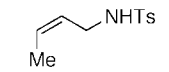
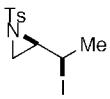
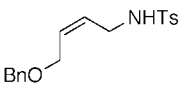
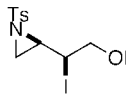
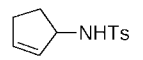
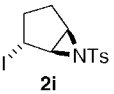
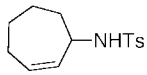
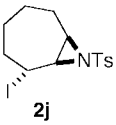
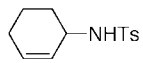
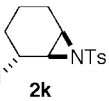
[a] Iodocyclization: **1** (1 mmol), *t*-BuOK (1.5 mmol), I_2 (3 mmol), toluene (5 mL), rt, 15 min. [b] Isolated yield.

the use of a strong base such as NaH or *t*-BuOK was found to be more effective (rntries 5, 6); especially, in the presence of *t*-BuOK (1.5 equiv) and I_2 (3 equiv), the reaction in toluene gave iodoaziridine **2a** in 94% yield (entry 6).[12] Although the remarkable effect of *t*-BuOK is not clear, it may act as not only an activating reagent for the enhancement of the nucleophilicity of tosylamide but also a neutralizing reagent for the trapping of HI. It was also found that 3 equiv of I_2 is required to obtain the iodoaziridine **2a** in good yield, while a decrease in the chemical yield was observed with the use of 1 or 2 equiv of I_2 (56% and 84%, respectively).

As shown in Table 2, a tosyl group was the most effective as a substituent on the nitrogen atom. For example, the reaction of mesylamide **1b** proceeded, but with a decrease in the chemical yield of **2b** (entry 2, 45%). Furthermore, in contrast to the sulfonylamides, the reaction of carbamate **1c** and benzamide **1d** did not result in the formation of the aziridine. With **1c**, an addition product of I_2 to the olefin was obtained as a major product (entry 3), while the reaction of **1d** under these conditions gave a five-membered ring compound (**3d**) in 90% yield through the attack of the amide carbonyl oxygen (entry 4).[13]

Iodoaziridination Reactions of Various *N*-Allylic Tosylamides. Table 3 contains a variety of *N*-allylic

Table 3. *t*-BuOK-Mediated Iodoaziridination of Various *N*-Allylic Tosyl Amides[a]

Entry	Amide **1**	Time (min)	Product **2**	Yield (%)[b]
1	 **1e**	15	 **2e**	90
2	 **1f**	15	 **2f**	74
3[c]	 ***E*-1g** (*E*/*Z*=3.6)[d]	15	 ***anti*-2g** (*syn*/*anti*=1/3.5)[d]	80
4[c]	 ***Z*-1g** (*E*/*Z*=1/3.7)[d]	15	 ***syn*-2g** (*syn*/*anti*=3.9)[d]	88
5	 ***Z*-1h** (*Z* only)	15	 ***syn*-2h** (*syn* only)	78
6[e]	 **1i**	30	 **2i**	92
7[e]	 **1j**	30	 **2j**	95
8[e]	 **1k**	30	 **2k**	63

[a] Iodocyclization: **1** (1 mmol), *t*-BuOK (1.5 mmol), I_2 (3 mmol), toluene (5 mL), rt. [b] Isolated yield. [c] The chemical structures of major isomers were drawn. [d] The ratios were determined by 300-MHz ^{1}H NMR. [e] 2 equiv of *t*-BuOK was used.

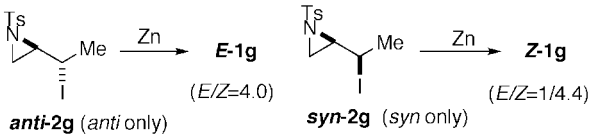
tosylamides (**1e**−**k**) subjected to the iodoaziridination conditions mentioned above [*t*-BuOK (1.5 equiv) and I_2 (3 equiv) in toluene]. As was found with allyl derivative **1a**, the reactions of methallyl and prenyl derivatives **1e**,**f** proceeded in good yields (90% and 74%, respectively) to give iodoaziridines **2e**,**f** (entries 1, 2). In the reaction of **1f**, the effect of *t*-BuOK was particularly noteworthy; that is, the use of NaH, which gave a good result in the reaction of **1a**, led to the formation of byproducts to result in a considerable decrease in the yield of **2f** (37%).

In the reactions of crotyl derivatives *E*-**1g** (*E*/*Z* = 3.6) and *Z*-**1g** (*E*/*Z* = 1/3.7), diastereomeric mixtures of aziridine **2g** were obtained in ratios of *syn*/*anti* = 1/3.5 and *syn*/*anti* = 3.9, respectively (entries 3, 4). The relative configurations of *syn*- and *anti*-**2g**, which can be easily separated by column chromatography, were determined by converting to crotyl derivative **1g** from *syn*- and *anti*-**2g** through *trans*-elimination by Zn, respectively

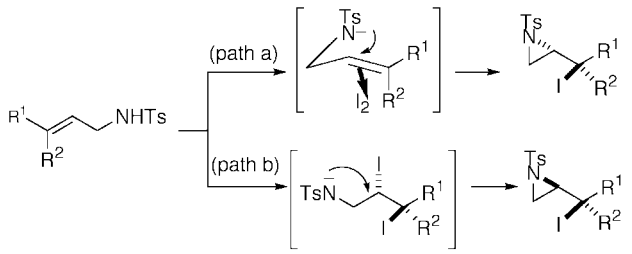
(12) Haloaziridine product could not be obtained by the combination of *t*-BuOK and NBS or NIS.

(13) Kitagawa, O.; Kikuchi, N.; Hanano, T.; Aoki, K.; Yamazaki, T.; Okada, M.; Taguchi, T. *J. Org. Chem.* **1995**, *60*, 7161.

Scheme 2



Scheme 3



(Scheme 2).[14] These results indicate that the present reaction proceeds through a stereospecific *trans*-addition of the amide nucleophile and iodine across the olefin (Scheme 3, path a), but not through an addition of iodine to the olefin and the subsequent substitution reaction of the iodide by the amide nucleophile (path b).[10a] In addition to the results of entries 3 and 4, the reaction of stereochemically pure *Z*-olefin **1h** with an oxygen functionality was found to give *syn*-**2h** as a single stereoisomer (entry 5); thus, the iodoaziridination reaction clearly proceeds with almost complete stereospecificity.

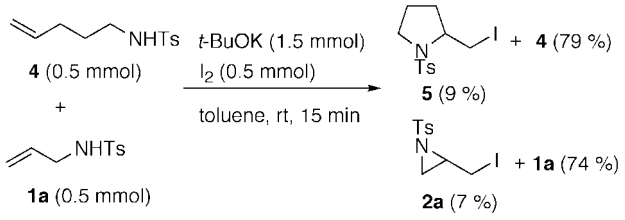
The present reaction can be also applied to *N*-cycloalkenyl tosylamide derivatives. For example, the reaction of cyclopentenyl and cycloheptenyl derivatives **1i**,**j** proceeded with complete stereoselectivity to give **2i**,**j** in greater than 90% yield (entries 6, 7). The reaction of cyclohexenyl derivative **1k** also gave iodoaziridine **2k** in 63% (entry 8). When NaH was used in the reaction of **1i**−**k** instead of *t*-BuOK, as was seen previously with **1f**, a marked decrease in the yields of **2i**−**k** was observed (**2i**, 45%; **2j**, 47%). In particular, the reaction of cyclohexenyl derivative **1k** hardly proceeded in the presence of NaH (**2k**, <5%).

In all the reactions shown here, the formation of a 4-*endo*-cyclized product was not observed, indicating the reactions proceed with complete 3-*exo*-selectivity.

We have also found that the rate of the iodoaziridination reaction is comparable with that of the corresponding five-membered ring-forming reaction.[15,16] As shown in Scheme 4, the reaction of *N*-allyl tosylamide **1a** (0.5 mmol) and *N*-pentenyl tosylamide **4** (0.5 mmol) gave iodoaziridine **2a** and iodopyrrolidine **5** in a ratio of 7:9 in the presence of *t*-BuOK (1.5 mmol) and I_2 (0.5 mmol). This result indicates that the three-membered ring-forming reaction in a halocyclization should be an efficient process similar to five- and six-membered ring-forming reactions.

It was also found that the iodoaziridine derivatives **2** formed in these reactions are relatively unstable under

Scheme 4



the reaction conditions; that is, product analysis by TLC monitoring indicates that prolonged reaction time leads to the decomposition of products **2** to give a complex mixture. The best yield in each reaction was obtained under the optimized reaction time shown in Table 3. On the other hand, all the aziridines **2** isolated can be stored at 0 °C for 1 week at least without appreciable decomposition.

In conclusion, we have succeeded in the development of a *t*-BuOK-mediated iodoaziridination reaction that proceeds with complete stereospecificity and regioselectivity (3-*exo* and *trans*-addition manner). The present reaction can be applied to a number of *N*-allylic tosylamide derivatives and provides a stereoselective synthesis of iodoaziridines with two consecutive chiral centers from simple *N*-allylic amides.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300-MHz spectrometer (Varian Gemini-300). In ^{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 (Hitachi M-80). Column chromatography was performed on silica gel, Wakogel C-200 (75−150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30- × 4-cm i.d. prepacked column (silica gel, 50 μm) with a UV detector.

Starting Materials. *N*-Allylic amides or carbamates **1a**−**d** were prepared in quantitative yields through reaction of allylamine with TsCl, MsCl, $ClCO_2Et$, or PhCOCl.[17] *N*-Allylic tosylamide derivatives **1e**−**h** and *N*-pentenyl tosylamide **4** were prepared from the corresponding bromides or chlorides according to reported procedures.[18] *N*-Cycloalkenyl tosylamides **1i**−**k** were prepared from the corresponding acetates according to reported procedures.[19]

General Procedure of Iodoaziridination. To tosylamide **1a** (212 mg, 1 mmol) in toluene (5 mL) was added *t*-BuOK (168 mg, 1.5 mmol) under an argon atmosphere at room temperature. The mixture was stirred for 30 min, and I_2 (762 mg, 3 mmol) was added. The reaction mixture was then stirred for 15 min at room temperature, was poured into aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/EtOAc = 9) gave **2a** (317 mg, 94%).[8]

(2*R,3*S**)- and (2*R**,3*R**)-*N*-Tosyl-1,2-imino-3-iodobutane (*anti*-2g and *syn*-2g).** *anti*- and *syn*-**2g** were prepared from *E*-**1g** (1.13 g, 5.0 mmol, *E*/*Z* = 3.6) in accordance with the general procedure described for **2a**. Purification of the residue by column chromatography (hexane/EtOAc = 9) gave *anti*-**2g** (1.09 g, 62%, less polar) and ***syn*-2g** (0.31 g, 18%, more polar). *anti*-**2g**: colorless solid; mp 67−69 °C; IR (KBr) 1326, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, d, *J* = 8.2 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 3.50 (1H, qd, *J* = 6.9, 9.5 Hz), 3.08 (1H, ddd, *J* = 4.4, 6.9, 9.5 Hz), 2.77 (1H, d, *J* = 6.9 Hz), 2.45 (3H, s), 2.13 (1H, d, *J* = 4.4 Hz),

(14) The incomplete stereospecificity observed in the *trans*-elimination of stereochemically pure *syn*- or *anti*-**2g** by Zn may be due to the contribution of a radical cleavage mechanism to some extent; See: Kimpe, N. D.; Jolie, R.; Smaele, D. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221.

(15) Examples of bromoaminocyclization of *N*-pentenyl or *N*-hexenyl amides: Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491.

(16) In the presence of *t*-BuOK and I_2, iodocyclization reaction of *N*-homoallyl tosylamide gave a mixture of 4-*exo*- and 5-*endo*-cyclized products in yields of 20% and 54%, respectively.

(17) Ginzberg, S. *Ber.* **1903**, *36*, 2703.

(18) (a) Gensler, W. J.; Frank, F. J.; Dheer, S. K.; Lauther, J. W. *J. Org. Chem.* **1971**, *36*, 4102. (b) Fugami, K.; Ohshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050.

(19) Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749.

1.73 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 144.8, 134.2, 129.6, 128.0, 47.1, 35.6, 25.6, 22.9, 21.6; MS (*m*/*z*) 351 (M^+), 224. Anal. Calcd for $C_{11}H_{14}INO_2S$: C, 37.60; H, 4.02; N, 3.99. Found: C, 37.74; H, 4.15; N, 3.95. *syn*-**2g**: colorless oil; IR (neat) 1327, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (2H, d, $J = 8.0$ Hz), 7.35 (2H, d, $J = 8.0$ Hz), 3.79 (1H, quint, $J = 7.1$ Hz), 3.07 (1H, m), 2.84 (1H, d, $J = 6.8$ Hz), 2.44 (3H, s), 2.25 (1H, d, $J = 4.1$ Hz), 1.79 (3H, d, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 144.8, 134.4, 129.6, 128.4, 46.9, 34.5, 23.9, 21.8, 21.6; MS (*m*/*z*) 351 (M^+), 224. Anal. Calcd for $C_{11}H_{14}INO_2S$: C, 37.60; H, 4.02; N, 3.99. Found: C, 37.72; H, 4.14; N, 3.99.

***Trans*-Elimination of *anti*-2g by Zn(0).** To a solution of *anti*-**2g** (948 mg, 2.7 mmol) in THF (15 mL) was added Zn dust (268 mg, 4.1 mmol) under argon atmosphere at room temperature. The mixture was stirred for 15 h at room temperature, and then the mixture was poured into aqueous NH_4Cl solution. After removal of insoluble material by filtration with a Celite pad, the filtrate was extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/EtOAc = 8) gave a mixture of *E*- and *Z*-**1g** (522 mg, 86%, $E/Z = 4.0$).

Competitive Experiment of Three- and Five-Membered Ring-Forming Reactions. To a mixture of *N*-allylic tosyl amide **1a** (106 mg, 0.5 mmol) and *N*-pentenyl tosylamide **4** (120 mg, 0.5 mmol) in toluene (5 mL) was addedd *t*-BuOK (168 mg, 1.5 mmol) under argon atmosphere at room temperature. The mixture was stirred for 30 min, and I_2 (127 mg, 0.5 mmol) was added. The reaction mixture was then stirred for 15 min at room temperature, poured into aqueous $Na_2S_2O_3$ solution, and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/EtOAc = 9) gave the mixture of **2a** (12 mg, 7%) and **5**[20] (16 mg, 9%) together with the recovery of **1a** (78 mg, 74%) and **4** (95 mg, 79%). The yields of **2a** and **5**[20] were determined on the basis of 300-MHz ^{1}H NMR of the mixture.

Supporting Information Available: Characterization data and experimental pocedures of **2a**,**b**,**e**,**f**, *syn*-**2h**, and **2i**−**k** (3 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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(20) Tseng, C.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1977**, *25*, 29.