

## Iodine Atom Transfer [3 + 2] Cycloaddition Reaction with Electron-Rich Alkenes Using *N*-Tosylidoaziridine Derivatives as Novel Azahomoallyl Radical Precursors

Osamu Kitagawa, Shinsaku Miyaji, Yoichiro Yamada, Hiroki Fujiwara, and Takeo Taguchi\*

Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

taguchi@ps.toyaku.ac.jp

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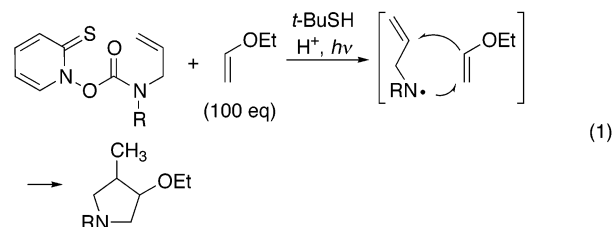
Treatment of *N*-tosylidoaziridine derivatives with Et<sub>3</sub>B efficiently produces various azahomoallyl radical (2-akenylamidyl radical) species which give oxygen-functionalized pyrrolidine derivatives through iodine atom transfer [3 + 2] cycloaddition with electron-rich alkenes such as enol ethers and ketene acetal. The present cycloaddition reaction proceeds regioselectively via C–N bond cleavage of an aziridinylalkyl radical intermediate and addition of the resulting azahomoallyl radicals to the terminal carbon of an alkene. The reaction of alkenes with the cyclohexenylamidyl radical generated from an optically active bicyclic iodoaziridine [(1*S*,2*S*,6*S*)-2-iodo-7-(*p*-toluenesulfonyl)-7-azabicyclo[4.1.0]heptane, 94% ee] also proceeds to give optically active octahydroindole derivatives (84–93% ee).

### Introduction

The [3 + 2] cycloaddition reaction of homoallyl radical (3-alkenyl radical) species with an alkene is well-known as a powerful means for one-step construction of a cyclopentane skeleton from simple substrates.<sup>1</sup> In contrast to many reports in relation to homoallyl radicals, the reaction of an azahomoallyl radical (2-alkenylaminyl radical), which should provide a useful synthetic method to pyrrolidine derivatives, has previously been reported in only one example.<sup>2</sup> Most of the reported reactions of nitrogen-centered radicals with an alkene have been limited to intramolecular 5-exo-cyclization of 4-pentenylaminyl radicals,<sup>3</sup> while the intermolecular reaction is uncommon.<sup>3,4</sup> This fact may be due to the lower reactivity of nitrogen-centered radicals in comparison with carbon-

centered radicals and the lack of a suitable radical precursor.<sup>3,5</sup>

In 1990, Newcomb et al. reported radical [3 + 2] cycloaddition with an alkene using an azahomoallyl radical species which was produced from *N*-allyl-*N*-hydroxypyridine-2-thione carbamate (PTOC carbamate) (eq 1).<sup>2</sup> As far as we know, this report is the only example



\* To whom correspondence should be addressed. Fax and Tel: +81-426-76-3257. E-mail: (O.K.) kitagawa@ps.toyaku.ac.jp.

(1) The reaction with electron-deficient alkenes: (a) Clieve, D. L. J.; Angoh, A. G. *J. Chem. Soc., Chem. Commun.* **1985**, 980–982. (b) Cekovik, Z.; Saicic, R. *Tetrahedron Lett.* **1986**, 27, 5893–5896. (c) Curran, D. P.; Chen, M. *J. Am. Chem. Soc.* **1987**, 109, 6558–6560. (d) Barton, D. H. R.; Zard, S. Z.; daSilva, E. *J. Chem. Soc., Chem. Commun.* **1988**, 285–287. (e) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, 110, 3300–3302. (f) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 779–831 and references therein. The reaction with simple alkenes: (g) Miura, K.; Fugami, K.; Ohshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, 29, 5135–5138. (h) Curran, D. P.; Chen, M.; Spletzer, E. *J. Am. Chem. Soc.* **1989**, 111, 8872–8878. (i) Chuang, C. P.; Hou, S. S.; Ngoi, T. H. *J. J. Chem. Res., Synop.* **1991**, 216–217. (j) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, 48, 2157–2174. (k) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, 48, 2175–2190. (l) Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435–1437. (m) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215–3229. (n) Kitagawa, O.; Fujiwara, H.; Taguchi, T. *Tetrahedron Lett.* **2001**, 42, 2165–2167. (o) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2002**, 67, 922–927. (p) Kitagawa, O.; Yamada, Y.; Sugawara, A.; Taguchi, T. *Org. Lett.* **2002**, 4, 1011–1013.

(2) Newcomb, M.; Kumar, M. U. *Tetrahedron Lett.* **1990**, 31, 1675–1678.

of the generation of an azahomoallyl radical and its annulation reaction. However, this method using PTOC carbamate still poses many problems: (1) a large excess (100 equiv) of the alkene partner is required to get the pyrrolidine product in reasonable yield (52–59%) because of lower reactivity of the allylaminyl radical; (2) since the application to alkenes other than enol ethers and reactions with other 2-alkenylaminyl radicals except for the allylaminyl radical were not investigated, the scope and limitation of the reaction are unclear; (3) addition of a

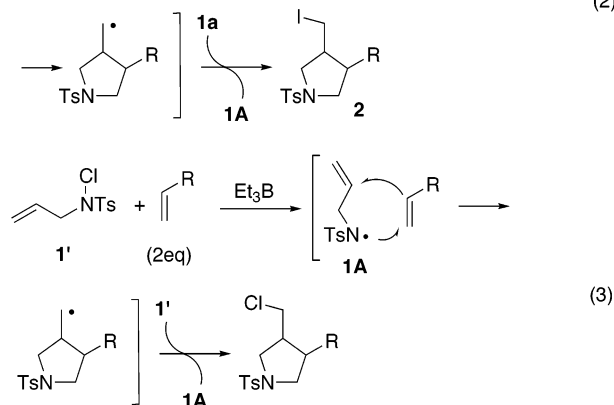
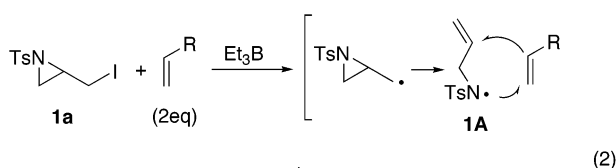
(3) For reviews, see: (a) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 337–350. (b) Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1993; Vol. 58, pp 1–45. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, 53, 17543–17593.

(4) For a review, see: Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, 34, 3241–3260.

(5) (a) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, 110, 6528–6535. (b) Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, 118, 3862–3868.

Brønsted acid for the generation of a more reactive allylaminium radical<sup>6</sup> and thiol as a hydrogen donor for the resulting pyrrolidinylmethyl radical are required; (4) further functionalization of the product should be difficult, because the resulting pyrrolidinylmethyl radical is trapped by the hydrogen atom transferred from the thiol. Thus, to achieve an efficient [3 + 2] cycloaddition reaction with an azahomoallyl radical, the development of a new precursor which generates a more reactive radical species may be required.

Quite recently, we and Oshima's group independently found that [3 + 2] cycloaddition of the *N*-tosyl-*N*-allylamidyl radical with electron-rich alkenes and styrene derivatives proceeds smoothly to give the pyrrolidine products in good yields (eq 2 and 3).<sup>7,8</sup> The success of these reactions may be due to the use of the respective (reactive) *N*-tosyl-*N*-allylamidyl radical generated from *N*-tosyloidoaziridine derivatives **1** and *N*-allyl-*N*-chlorosulfonylamide **1'**.



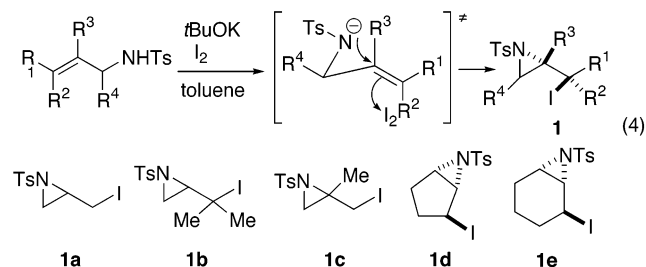
Oshima's method using *N*-allyl-*N*-chlorosulfonylamide **1'** affords the reaction with various styrene derivatives to proceed efficiently to give the [3 + 2] cycloaddition products in excellent yields, while with an electron-rich alkene such as an enol ether, a considerable decrease in the chemical yield is observed (eq 3).<sup>8</sup> The reaction with other 2-alkenylamidyl radicals was not investigated except for that with the allylamidyl radical. On the other hand, although our method using *N*-tosyloidoaziridine derivatives **1** still has some problems to be solved in the reaction with alkyl-substituted alkenes and styrene derivatives (vide infra), various azahomoallyl radicals

such as allyl-, prenyl-, and cycloalkenylamidyl radicals could be easily generated from the precursors, and the [3 + 2] cycloaddition reaction with electron-rich alkenes proceeded efficiently (eq 2).<sup>7</sup>

We report in detail an iodine atom transfer [3 + 2] cycloaddition reaction with electron-rich alkenes using various *N*-tosyloidoaziridine derivatives as new azahomoallyl radical precursors. The reaction with an azahomoallyl radical species generated from an optically active iodoaziridine derivative is also described.

## Results and Discussion

**Concept of the Reaction.** We previously reported that iodomethylcyclopropane derivatives having two electron-withdrawing groups on the ring effectively work as allylated active methine radical precursors, and the iodine atom transfer [3 + 2] cycloaddition of these with various alkenes proceeds to give the iodoalkylated cyclopentane derivatives in good yields.<sup>11–13</sup> As new azahomoallyl radical precursors, *N*-tosyloidoaziridine derivatives **1** having a similar iodoalkylated three-membered ring skeleton attracted our attention for the following reasons: (1) when **1a** is treated with a suitable radical initiator, azahomoallyl radical species **1A** might be efficiently generated via regioselective cleavage of the C–N bond of an aziridinylmethyl radical intermediate (eq 2);<sup>9</sup> (2) the reaction of **1A** with an alkene would possibly give an iodoalkylated pyrrolidine derivative through an iodine atom-transfer mechanism (eq 2);<sup>10</sup> (3) since it is well-known that the reactivity of a nitrogen-centered radical toward an alkene increases with decreasing electron density on the nitrogen atom,<sup>6</sup> the *N*-tosylamidyl radical may show higher reactivity than a simple aminyl radical;<sup>11</sup> (4) the mild conditions for the generation of **1A** and its addition to alkenes would make it possible to use a wide range of alkenes; (5) the generation of other 2-alkenylamidyl radicals in addition to a simple allylamidyl radical may also be possible, because various iodoaziridine derivatives **1a–1e** can be easily prepared through an iodoaziridination reaction of *N*-allyl-*N*-tosylamide derivatives, previously reported by our group (eq 4).<sup>12</sup>



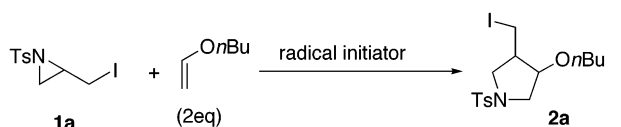
(6) It has been well-known that electrophilic aminium cation radicals and metal-complexed aminyl radicals formed by the addition of Brønsted acid and Lewis acid are more reactive to alkenes than simple aminyl radicals. (a) Neals, R. S.; Marcus, N. L. *J. Org. Chem.* **1967**, *32*, 3273–3284. (b) Surzur, J. M.; Stella, L.; Tordo, P. *Bull. Soc. Chim. Fr.* **1970**, 115–120. (c) Neale, R. S. *Synthesis* **1971**, 1–15. (d) Dickinson, J. M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 434–436. (e) Ha, C.; Musa, O.; Martinez, M. F.; Newcomb, M. *J. Org. Chem.* **1997**, *32*, 2704–2710. (f) Hemmerling, M.; Sjöholm, A.; Somfai, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4091–4094 and references therein.

(7) Our preliminary communication: Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3865–3867.

(8) Tsuritani, T.; Shinokubo, H.; Ohshima, K. *Org. Lett.* **2001**, *3*, 2709–2711.

(9) Reports in relation to regioselective cleavage of aziridinylcarbonyl radicals and their application to intramolecular radical cyclization: (a) Dickinson, J. M.; Murphy, J. A. *Tetrahedron* **1992**, *48*, 1317–1326. (b) De Kimpe, N.; Jolie, R.; De Smaele, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221–1222. (c) De Smaele, D.; Bogaert, P.; De Kimpe, N. *Tetrahedron Lett.* **1998**, *39*, 9797–9800. For a review, see: (d) Li, J. J. *Tetrahedron* **2001**, *57*, 1–24.

(10) Since the formation of an aziridinyl methyl radical is a thermodynamically favorable process, an iodine-transfer process leading to the resulting pyrrolidinyl methyl radical intermediate from iodoaziridine **1** should proceed efficiently.

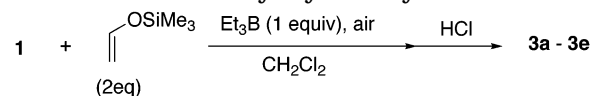
**TABLE 1. Radical [3 + 2] Cycloaddition of Iodoaziridines **1a** with Enol Ethers**

Entry	Initiator	Solvent	Temp.	Yield [%] <sup>a</sup>	<i>cis/trans</i> <sup>b</sup>
1	AIBN	C <sub>6</sub> H <sub>6</sub>	80 °C	0	-
2	0.2 equiv ( <i>n</i> Bu <sub>3</sub> Sn) <sub>2</sub> , <i>hν</i>	C <sub>6</sub> H <sub>6</sub>	rt	48	1.1
3	1 equiv Et <sub>3</sub> B	C <sub>6</sub> H <sub>6</sub>	rt	62	1.0
4	1 equiv Et <sub>3</sub> B	CH <sub>2</sub> Cl <sub>2</sub>	rt	64	1.0
5	1 equiv Et <sub>3</sub> B	THF	rt	22	1.0

<sup>a</sup> Yield of isolated product. <sup>b</sup> The ratio was determined by 300 MHz <sup>1</sup>H NMR.

**[3 + 2] Cycloaddition of Various Azahomoallyl Radicals with Vinyl Ether Derivatives.** Initially, the [3 + 2] cycloaddition of **1a** with butyl vinyl ether (2 equiv) was investigated under several free-radical iodine atom transfer conditions [Et<sub>3</sub>B/O<sub>2</sub>, (*n*-Bu<sub>3</sub>Sn)<sub>2</sub>/*hν*, AIBN/Δ] (Table 1). The reaction with 1 equiv of Et<sub>3</sub>B<sup>13</sup> in C<sub>6</sub>H<sub>6</sub> or CH<sub>2</sub>Cl<sub>2</sub> gave good results; thus, 3-butoxy-4-iodomethylpyrrolidine **2a** was obtained in 62% and 64% yield, respectively (entries 3, 4).

Under the optimized conditions [enol ether (2 equiv), Et<sub>3</sub>B (1 equiv), 0.13 M **1a** in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 10 h], the cycloaddition reaction with various azahomoallyl radicals was further examined (Table 2). Since the present reaction using Et<sub>3</sub>B proceeds under mild conditions, application to vinyloxytrimethylsilane, which can be easily deprotected at the product stage, is also possible. The reaction with **1a** followed by treatment with HCl gave desilylated 3-hydroxy-4-iodomethylpyrrolidine **3a** in 66% yield (entry 1).<sup>14</sup> The reaction of silyl enol ether with other iodoaziridines **1b** and **1c** which produce prenyl- and methallyl-amidyl radicals also proceeded smoothly (entries 2, 3). In the reaction with **1b**, the unstable product (*tert*-iodide) was treated with DBU and alkenyl product **3b** was isolated in 63% yield (entry 2). With **1c**, a mixture of iodine atom transfer product **3c** and reduced product **3c'** was obtained in a ratio of 3.8:1 (67% yield) (entry 3). Although the formation of such reduced product was also observed in the reaction of **1a** with butyl vinyl ether and vinyloxytrimethylsilane, the yields were less than 5%. In the reaction with bicyclic iodoaziridines **1d** and **1e** which leads to cycloalkenyl amidyl radicals, bicyclic nitrogen-containing compounds such as hydrocyclopentapyrrole **3d** and hydroindole **3e**

**TABLE 2. Radical [3 + 2] Cycloaddition of Various Iodoaziridines **1** with Vinyloxytrimethylsilane**

Entry	Aziridine	Product	Yield [%] <sup>a</sup>	<i>cis/trans</i> <sup>b</sup>
1	<b>1a</b>	<b>3a</b>	66	1.3
2 <sup>c</sup>	<b>1b</b>	<b>3b</b>	63 <sup>d</sup>	-
3	<b>1c</b>	<b>3c</b> (X=I) <b>3c'</b> (X=H) <b>3c/3c'</b> =3.8	67	4.3
4	<b>1d</b>	<b>3d</b>	60	1.5 (α-OH/β-OH)
5	<b>1e</b>	<b>3e</b>	62	1/1.4 (α-OH/β-OH)

<sup>a</sup> Yield of isolated product. <sup>b</sup> The ratio was determined on the basis of isolated products. <sup>c</sup> The product (*tert*-iodide) was subsequently treated with DBU. <sup>d</sup> A mixture of internal double bond product and terminal double bond product was obtained in a ratio of 4:1.

were obtained in 60% and 62% yields, respectively (entries 4 and 5).

All reactions shown in Tables 1 and 2 were performed in the presence of 2 equiv of alkenes to yield the products at a synthetically useful level. Unfortunately, the stereoselectivities were generally low; the products **3a–e** were obtained with *cis/trans* ratios in the range of 1–4.3.<sup>15</sup> In the reaction with bicyclic iodoaziridines **1d** and **1e**, among four or eight possible diastereomers, two diastereomers based on α- and β-OH were produced in low diastereoselectivity (α-**3d**/β-**3d** = 1.5, α-**3e**/β-**3e** = 1/1.4) (entries 4 and 5).<sup>15,16</sup> On the other hand, the formation of a regioisomer was not observed in all reactions. Thus, both cleavage of the C–N bond in the *N*-tosylaziridinylalkyl radical and the attack of the resulting *N*-tosylamidyl radical on the terminal carbon atom of the alkene proceeded with complete regioselectivity.

**[3 + 2] Cycloaddition of Azahomoallyl Radicals with Various Electron-Rich Alkenes.** Iodine atom transfer [3 + 2] cycloaddition of azahomoallyl radicals with various electron-rich alkenes was conducted in the

(15) The stereochemistries of the products were determined on the basis of NOESY measurement. In addition, comparison of the <sup>13</sup>C chemical shift of the iodomethyl group is also useful for the determination of the stereochemistry. For example, the chemical shift of the iodomethyl group in *cis*-isomers of **2a**, **3a**, **3b**, **4a**, and **8a** appears upfield from that of *trans*-isomers.

(16) In the preliminary communication (ref 7), the diastereomer ratio (α-**2d**/β-**2d** = 1/1.5, α-**2e**/β-**2e** = 1.4) which corresponds to compound **3d** and **3e** in this paper, was found to be a typographical errors due to our carelessness. As shown in entries 4 and 5 of Table 2, we must now correct the ratio as α-**2d**/β-**2d** = 1.5 and α-**2e**/β-**2e** = 1/1.4 in ref 7.

(11) Horner, J. H.; Musa, O.; Bouvier, M. A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738–7748.

(12) Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 4842–4845.

(13) Oshima, K.; Uchimoto, K. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 40–50.

(14) In the reaction of **1a** with silyl enol ether, (*n*-Bu<sub>3</sub>Sn)<sub>2</sub> gave a better result than Et<sub>3</sub>B. That is, under irradiation of a sunlamp, when to the benzene solution of **1a** and silyl enol ether was added (*n*-Bu<sub>3</sub>-Sn)<sub>2</sub> in portionwise (0.1 equiv × 3), the product **3a** was obtained in 80% yield. However, in the reaction with other iodoaziridines and alkenes, this method resulted in the decrease in the chemical yield in comparison with the Et<sub>3</sub>B-mediated method.

**TABLE 3. Radical [3 + 2] Cycloaddition of Various Iodoaziridines **1** with Various Alkenes**

aziridines <b>1</b>		+	alkenes	$\xrightarrow[\text{C}_6\text{H}_6]{\text{Et}_3\text{B, air}}$	products <b>4</b> - <b>8</b>	Yield [%] <sup>a</sup>	<i>cis/trans</i> <sup>b</sup>
1	<b>1a</b>					71	1/1.7
2	<b>1a</b>					62	- <sup>c</sup>
3	<b>1a</b>					62	-
4	<b>1d</b>					64	- <sup>c</sup>
5	<b>1e</b>					59	- <sup>c</sup>
6 <sup>d</sup>	<b>1a</b>					56	-
7 <sup>d</sup>	<b>1a</b>					34	2.1 <sup>e</sup>

<sup>a</sup> Yield of isolated product. <sup>b</sup> The ratio was determined on the basis of isolated products. <sup>c</sup> Other stereoisomers were not detected. <sup>d</sup> The reaction was carried out by portionwise addition of Et<sub>3</sub>B (3 × 0.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub>. <sup>e</sup> The ratio was determined by 300 MHz <sup>1</sup>H NMR.

presence of Et<sub>3</sub>B (1 equiv) (Table 3). In addition to vinyl ethers, other enol ethers such as 2-propenyl methyl ether and 2,3-dihydrofuran also reacted efficiently (entries 1, 2). The reaction of **1a** with 2-propenyl methyl ether (2 equiv) gave the products *cis*- and *trans*-**4a** in good yield (71%) but in low diastereoselectivity (*cis*-**4a**/*trans*-**4a** = 1/1.7) (entry 1). In the reaction of **1a** with 2,3-dihydrofuran (2 equiv), bicyclic products **5a**, **5a'** having an *endo*-iodomethyl or *endo*-methyl group were obtained with complete stereoselectivity in 62% yield (entry 2).<sup>15</sup> Such high *endo* selectivity is also observed in the reaction of a homoallyl radical species with cyclopentene and 2,3-dihydrofuran.<sup>10,17</sup> In these reactions, high concentration conditions (1 M **1a** in C<sub>6</sub>H<sub>6</sub>) were required for complete consumption of **1a**.

The present reaction can be applied not only to enol ethers but also ketene acetals. For example (Table 3), the reaction of **1a** with a ketene acetal (2 equiv) in C<sub>6</sub>H<sub>6</sub> gave [3 + 2] cycloadducts **6a** in 62% yield (entry 3). In CH<sub>2</sub>-Cl<sub>2</sub>, a slight decrease in the chemical yield was observed (**6a**: 56%). The reaction of bicyclic iodoaziridines **1d** and

(17) The model to rationalize such *endo* selectivity in the bicyclo-[3.3.0]octane system has been reported by Curran and co-workers: Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943–3953.

**1e** with the ketene acetal afforded bicyclic nitrogen-containing compounds **6d** and **6e** in 64% and 59% yields, respectively (entries 4, 5). With **1d**, a considerable amount (28%) of reduced product **6d'** was isolated together with an iodine atom transfer product **6d** (36%) (entry 4). In both cases of **1d** and **1e**, the formation of other stereoisomers was not observed.<sup>15</sup> These results indicate that in the reaction of a cycloalkenylamidyl radical with alkenes, the 5-*exo*-cyclization leading to a *cis*-fused ring system and subsequent iodination of the cycloalkyl radicals from the convex (*exo*) side proceed with almost complete stereoselectivity (see also entries 4, 5 in Table 2).

With alkyl-substituted alkenes, considerable decrease in the chemical yield was observed. For example, under the above conditions, the reaction of **1a** with methylenecyclohexane gave the product **7a** in low yield (28%), and *N*-allyltosylamide was formed as a side product. This result may indicate that the reactivity of the *N*-tosylamidyl radical toward the alkene decreases with decreasing electron richness of the alkene. Indeed, 1-hexene, with lower electron density in comparison with 1,1-disubstituted alkene, did not give the product. On the other hand, it was found that gradual generation of an *N*-tosylamidyl radical by portionwise addition of Et<sub>3</sub>B (3 × 0.5 equiv) led to increase in product yield.<sup>18</sup> The reaction with methylenecyclohexane and with 1-hexene by this procedure gave the products **7a** and **8a** in 56% and 34% yield, respectively (entries 6, 7). Although the reaction of **1a** with styrene which gave a good result by Oshima's method was also investigated, the yield of the [3 + 2] cycloadduct was very minor. Similar to the reactions in Tables 1 and 2, no regioisomer was detected in any of reactions shown in Table 3.

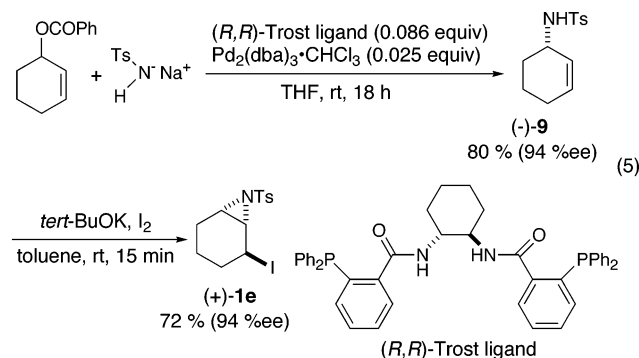
**Generation and [3 + 2] Cycloaddition of Optically Active Cyclohexenylamidyl Radical.** An octahydroindole skeleton is an important basic structure of several natural alkaloids.<sup>19</sup> We expected that the asymmetric synthesis of an octahydroindole skeleton might also be possible through the reaction of an alkene with a cyclohexenylamidyl radical produced from optically active iodoaziridine **1e**. Optically active (+)-**1e** could be prepared in accordance with eq 5. That is, catalytic asymmetric tosylation of 2-cyclohexenyl benzoate by Trost's method<sup>20</sup> and subsequent iodoaziridination<sup>12</sup> of the resulting *N*-tosylcyclohexenylamide (–)-**9** gave (+)-**1e** in 57% overall yield. *Ee* values of both (–)-**9** and (+)-**1e** were estimated to be 94% by HPLC analysis using a CHIRALPACK AS column. Thus, it is obvious that iodoaziridination of (–)-**9** proceeds without any racem-

(18) **Caution:** When Et<sub>3</sub>B was added to the reaction mixture under high concentration of O<sub>2</sub>, we once experienced an explosion. Thus, further addition of Et<sub>3</sub>B must be performed under Ar or N<sub>2</sub> atmosphere.

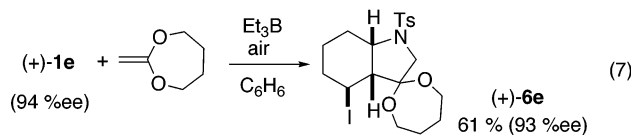
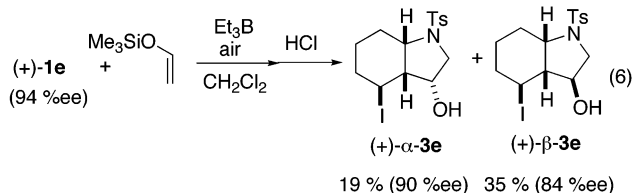
(19) Recent reports in relation to hydroindole alkaloids: (a) Banker, R.; Carmeli, S. *Tetrahedron* **1999**, *55*, 10835–10844. (b) Valls, N.; Vallribera, M.; López-Canet, M.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 4945–4950. (c) Ishida, K.; Okita, H.; Matsuda, H.; Okino, T.; Murakami, M. *Tetrahedron* **1999**, *55*, 10971–10988. (d) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem. Eur. J.* **2001**, *7*, 3446–3460. (e) Wipf, P.; Methot, J.-L. *Org. Lett.* **2000**, *2*, 4231–4216. (f) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724. (g) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537–5545.

(20) (a) Trost, B. M.; Vranken, D. L. V.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343. (b) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339–1341. (c) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591.

ization. The absolute stereochemistry was determined by comparison of the  $[\alpha]_D$  value with the reported values of **9**.<sup>21</sup>



Similar to that of racemic **1e**, the reaction of (+)-**1e** (94% ee) with silyl enol ether gave a diastereomeric mixture of cycloadduct (+)-**3e** in 54% yield (eq 6). Surprisingly, decrease in the ee of each diastereomeric product,  $\alpha$ -(+)-**3e** (90%ee) and  $\beta$ -(+)-**3e** (84%ee), was observed. The same result was obtained in each of the three reactions attempted. The degree of racemization strongly depends on the kind of alkene counterpart. For example, the reaction of (+)-**1e** (94%ee) with ketene acetal gave optically active product (+)-**6e** in 93%ee (61% yield) (eq 7). This result suggests that the degree of such racemization depends on the nature of the alkene.



Partial racemization may be brought about by hydrogen abstraction by radical intermediate **1EA** (Figure 1). That is, after addition of cyclohexenylamidyl radical **1E** to alkene, the resulting radical intermediate **1EA** has an active allylic hydrogen which is located at the appropriate position for the abstraction by the radical. Moreover, it has been reported that 5-*exo*-cyclization of an alkoxy-carbon radical is slower in comparison with that of a simple carbon radical.<sup>8</sup> Therefore, in the reaction with silyl enol ether, allylic hydrogen abstraction (**1EB** from **1EA**) may competitively occur together with 5-*exo*-cyclization (**1EC** from **1EA**). We assume that the hydrogen abstraction process (**1EA** and **1EB**) is in equilibrium to form racemized **1EA** from **1EB** in part, by which the partial racemic product **6e** was resulted.

In conclusion, we have succeeded in developing a radical iodine atom transfer [3 + 2] cycloaddition reaction with electron-rich alkenes using various iodoaziridines

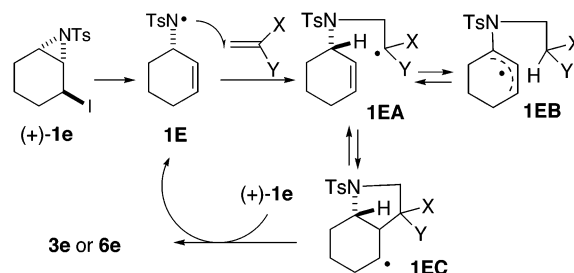


FIGURE 1. Possible mechanism of partial racemization.

as novel precursors of azahomoallyl radicals. Although there are still problems to address in the reaction with alkyl-substituted alkenes, the reaction described here should provide new and efficient methodology for the synthesis of oxygen-functionalized pyrrolidine derivatives.

## Experimental Section

Melting points were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 300-MHz spectrometer. In <sup>1</sup>H and <sup>13</sup>C NMR spectra, chemical shifts were expressed in  $\delta$  (ppm) downfield from CHCl<sub>3</sub> (7.26 ppm) and CDCl<sub>3</sub> (77.0 ppm), respectively. Mass spectra were recorded by electron impact or chemical ionization. Column chromatography was performed on silica gel (75–150  $\mu$ m). Medium-pressure liquid chromatography (MPLC) was performed on a 30  $\times$  4 cm i.d. prepacked column (silica gel, 50  $\mu$ m) with a UV detector. High-performance liquid chromatography (HPLC) was performed on a 25  $\times$  0.4 cm i.d. chiral column with a UV detector.

**Starting Materials.** Iodoaziridine derivatives **1a–e** were prepared through iodoaziridination of *N*-allyl tosylamide derivative which was previously reported by our group.<sup>12</sup>

**cis- and trans-N-(*p*-Toluenesulfonyl)-3-*n*-butoxy-4-iodomethylpyrrolidine (cis-**2a** and trans-**2a**).** Et<sub>3</sub>B (0.5 mL, 1 M hexane solution) was added to a solution of iodoaziridine **1a** (169 mg, 0.5 mmol) and butyl vinyl ether (0.13 mL, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) under Ar atmosphere. Dry air (20 mL) was subsequently introduced with a syringe. After the mixture was stirred for 10 h at room temperature, aqueous NH<sub>4</sub>Cl solution (4 mL) was added, and the mixture was extracted with Et<sub>2</sub>O. The extracts were washed with brine, dried over MgSO<sub>4</sub>, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 20) gave a mixture of pyrrolidine *cis*-**2a** and *trans*-**2a** (141 mg, 64%, *cis/trans* = 1). The inseparable mixture of *cis*-**2a** and *trans*-**2a** was converted to 4-methylenepyrrolidine derivative **2a'** in accordance with the following procedure.

**N-(*p*-Toluenesulfonyl)-3-*n*-butoxy-4-methylenepyrrolidine (**2a**).** DBU (0.05 mL, 0.36 mmol) was added to a solution of the mixture (131 mg, 0.3 mmol) of *cis*-**2a** and *trans*-**2a** in DMF (4 mL). After being stirred for 8 h at 80  $^{\circ}$ C, the mixture was poured into 2% HCl and extracted with Et<sub>2</sub>O. The extracts were worked up as noted above. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave **2a'** (88 mg, 95%). **2a'**: colorless solid; mp 51–52  $^{\circ}$ C; IR (KBr) 1346, 1161 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.71 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.17 (m, 1H), 5.11 (m, 1H), 4.12 (m, 1H), 3.91 (d, *J* = 13.8 Hz, 1H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.60 (dd, *J* = 5.2, 10.2 Hz, 1H), 3.26–3.42 (m, 2H), 3.18 (dd, *J* = 3.0, 10.2 Hz, 1H), 2.41 (s, 3H), 1.36–1.48 (m, 2H), 1.18–1.22 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  143.7, 143.5, 133.0, 129.5, 127.7, 110.9, 78.6, 68.6, 53.5, 50.3, 31.6, 21.4, 19.1, 13.7; MS (*m/z*) 309 (M<sup>+</sup>); HRMS calcd for C<sub>16</sub>H<sub>24</sub>NO<sub>3</sub>S (M<sup>+</sup> + 1) 310.1477, found 310.1456.

**cis- and trans-N-(*p*-Toluenesulfonyl)-3-hydroxy-4-iodomethylpyrrolidine (cis-**3a** and trans-**3a**).** Et<sub>3</sub>B (0.5 mL, 1 M hexane solution) was added to a solution of iodoaziridine **1a** (169 mg, 0.5 mmol) and trimethylsilyl vinyl ether (0.15

(21) (a) Müller, P.; Nury, P. *Helv. Chim. Acta* **2001**, *84*, 662–678. (b) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339–3342.

mL, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) under Ar atmosphere. Dry air (20 mL) was subsequently introduced with a syringe. After the mixture was stirred for 10 h at room temperature, 5% HCl (4 mL) and MeOH (15 mL) were added, and the mixture was then stirred for 2 h at room temperature. The MeOH was removed by evaporation, the residue was extracted with Et<sub>2</sub>O, and the extracts were worked up as noted above. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave a mixture of *cis*-**3a** and *trans*-**3a**. Further purification of the mixture by MPLC (hexane/AcOEt = 2) gave *cis*-**3a** (71 mg, 37%, less polar) and *trans*-**3a** (56 mg, 29%, more polar), respectively. *cis*-**3a**: colorless solid; 130–131 °C; IR (KBr) 3492, 1322, 1152 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.31 (q, *J* = 3.8 Hz, 1H), 3.60 (dd, *J* = 7.9, 9.6 Hz, 1H), 3.51 (dd, *J* = 3.8, 11.6 Hz, 1H), 3.43 (dd, *J* = 1.0, 11.6 Hz, 1H), 3.17 (dd, *J* = 9.0, 9.8 Hz, 1H), 3.10 (dd, *J* = 6.8, 9.8 Hz, 1H), 3.01 (dd, *J* = 9.6, 10.6 Hz, 1H), 2.44 (s, 3H), 2.42 (m, 1H), 1.59 (d, *J* = 4.9 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 143.7, 133.5, 129.7, 127.3, 71.1, 56.3, 50.8, 47.2, 21.4, 0.3; MS *m/z* 381 [M<sup>+</sup>]; HRMS calcd for C<sub>12</sub>H<sub>16</sub>INO<sub>3</sub>S [M<sup>+</sup>] 380.9896, found 380.9869. *trans*-**3a**: colorless solid; 136–137 °C; IR (KBr) 3501, 1338, 1160 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.05 (m, 1H), 3.56 (dd, *J* = 5.9, 10.5 Hz, 1H), 3.51 (dd, *J* = 7.5, 10.5 Hz, 1H), 3.05–3.15 (m, 3H), 2.97 (dd, *J* = 7.8, 10.5 Hz, 1H), 2.44 (s, 3H), 2.28 (m, 1H), 2.17 (brs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 144.0, 132.8, 129.9, 127.5, 74.6, 54.3, 52.2, 48.7, 21.6, 4.9; MS (*m/z*) 381 (M<sup>+</sup>); HRMS calcd for C<sub>12</sub>H<sub>16</sub>INO<sub>3</sub>S (M<sup>+</sup>) 380.9896, found 380.9877.

***N*-(*p*-Toluenesulfonyl)-4-iodomethyl-2-azaspiro[4.5]-decane (7a).** Under Ar atmosphere, to a solution of iodoaziridine **1a** (510 mg, 1.5 mmol) and methylenecyclohexane (0.36 mL, 3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was added Et<sub>3</sub>B (2.25 mL, 1 M hexane solution) portionwise (0.75 mL, every 30 min). Dry air (20 mL) was subsequently introduced with a syringe. After the mixture was stirred for 2 h at room temperature, saturated aqueous NH<sub>4</sub>Cl (12 mL) solution was added, and the mixture was then extracted with Et<sub>2</sub>O. The extracts were worked up as noted above. Purification of the residue by column chromatography (hexane/AcOEt = 30) gave **7a** (364 mg, 56%). **7a**: colorless oil; IR (neat) 1343, 1161 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.68 (dd, *J* = 7.5, 10.2 Hz, 1H), 3.46 (d, *J* = 10.2 Hz, 1H), 3.19 (dd, *J* = 3.4, 9.7 Hz, 1H), 3.11 (dd, *J* = 8.2, 9.7 Hz, 1H), 3.02 (d, *J* = 10.2 Hz, 1H), 2.71 (t, *J* = 10.2 Hz, 1H), 2.44 (s, 3H), 2.12 (m, 1H), 1.40–1.63 (m, 4H), 1.00–1.40 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 143.4, 133.7, 129.6, 127.3, 56.4, 53.1, 51.2, 45.6, 35.3, 28.2, 25.7, 23.3, 22.4, 21.5, 3.2; MS (*m/z*) 433 (M<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>INO<sub>2</sub>S: C, 47.12; H, 5.58, N, 3.23. Found: C, 47.52; H, 5.65, N, 3.24.

**(*S*)-*N*-(*p*-Toluenesulfonyl)cyclohexenylamine [(−)-9].** NaH (60% assay, 250 mg, 6.25 mmol) was added to the tosylamide (1.285 g, 7.50 mmol) in THF (25 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature, 3-cyclohexenyl benzoate (1.01 g, 5 mmol) was added to the mixture. Trost ligand (300 mg, 0.43 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (128 mg, 0.12 mmol) in THF (5 mL) were subsequently added, and then the mixture was stirred for 18 h at room temperature. The mixture was poured into water and extracted with Et<sub>2</sub>O. The extracts were worked up as noted above. Purification of the residue by column chromatography (hexane/AcOEt = 10)

gave (−)-**9** (1.01 g, 80%, 94% ee). The ee (94% ee) of (−)-**9** was determined by HPLC analysis using CHIRALPACK AD column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**9** (minor); *t*<sub>R</sub> = 13.5 min, (−)-**9** (major); *t*<sub>R</sub> = 14.5 min]. (−)-**9**: [α]<sub>D</sub> = −80.0 (*c* = 1.5, CHCl<sub>3</sub>).<sup>21</sup> <sup>1</sup>H NMR data of (−)-**9** coincided with those reported in the literature.<sup>21a</sup>

**(1*S*,2*S*,6*S*)-2-Iodo-7-(*p*-toluenesulfonyl)-7-azabicyclo[4.1.0]heptane [(+)-1e].** (+)-**1e** was prepared from (−)-**9** (1.0 g, 4 mmol) in accordance with the procedure of our iodoaziridination method.<sup>12</sup> Purification of the residue by column chromatography (hexane/AcOEt = 10) gave (+)-**1e** (1.09 g, 72%, 94% ee). The ee (94% ee) of (+)-**1e** was determined by HPLC analysis using CHIRALPACK AS column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-**1e** (minor); *t*<sub>R</sub> = 8.5 min, (+)-**1e** (major); *t*<sub>R</sub> = 9.9 min]. [α]<sub>D</sub> = +57.2 (*c* = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR data of (+)-**1e** coincided with those reported in the literature.<sup>12</sup>

**(3*S*,3*aR*,4*S*,7*aS*)- and (3*R*,3*aR*,4*S*,7*aS*)-*N*-(*p*-Toluenesulfonyl)-4-iodooctahydro-1*H*-indol-3-ol [(+)-β-3e and (+)-α-3e].** (+)-**3e** was prepared from iodoaziridine **1e** (377 mg, 1.0 mmol) and trimethylsilyl vinyl ether (0.3 mL, 2 mmol) in accordance with the procedure for the preparation of **3a**. Purification of the residue by column chromatography (hexane/AcOEt = 1) gave a mixture of (+)-β-**3e** and (+)-α-**3e**. Further purification of the mixture by MPLC (hexane/AcOEt = 2) gave (+)-β-**3e** (147 mg, 35%, less polar) and (+)-α-**3e** (80 mg, 19%, more polar), respectively. The ee (84% ee) of (+)-β-**3e** was determined by HPLC analysis using CHIRALPACK AD column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-β-**3e** (minor); *t*<sub>R</sub> = 14.7 min, (+)-β-**3e** (major); *t*<sub>R</sub> = 16.4 min]. The ee (90% ee) of (+)-α-**3e** was determined by HPLC analysis using CHIRALPACK AD column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-α-**3e** (minor); *t*<sub>R</sub> = 11.7 min, (+)-α-**3e** (major); *t*<sub>R</sub> = 14.8 min]. (+)-β-**3e**: [α]<sub>D</sub> = +66.1 (*c* = 1.0, CHCl<sub>3</sub>). (+)-α-**3e**: [α]<sub>D</sub> = +79.2 (*c* = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR data of (+)-β-**3e** and (+)-α-**3e** coincided with those of racemic β-**3e** and α-**3e** (see the Supporting Information).

**[(+)-6e].** (+)-**6e** was prepared from iodoaziridine **1e** (189 mg, 0.5 mmol) and ketene acetal (63 mg, 0.55 mmol) in accordance with the procedure for the preparation of **2a**. Purification of the residue by column chromatography (hexane/AcOEt = 10) gave (+)-**6e** (150 mg, 61%, 93% ee). The ee (93% ee) of (+)-**6e** was determined by HPLC analysis using CHIRALPACK AD column [25 cm × 0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-**6e** (minor); *t*<sub>R</sub> = 11.2 min, (+)-**6e** (major); *t*<sub>R</sub> = 17.4 min]. (+)-**6e**: [α]<sub>D</sub> = +50.4 (*c* = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR data of (+)-**6e** coincided with those of racemic **6e** (see the Supporting Information).

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**Supporting Information Available:** Experimental procedures for the preparation and characterization data of products **3b–e**, **4a**, **5a**, **6a,d,d',e**, and **8a,a'**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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