Optically Active Axially Chiral Anilide and Maleimide Derivatives as New Chiral Reagents: Synthesis and Application to Asymmetric Diels−Alder Reaction

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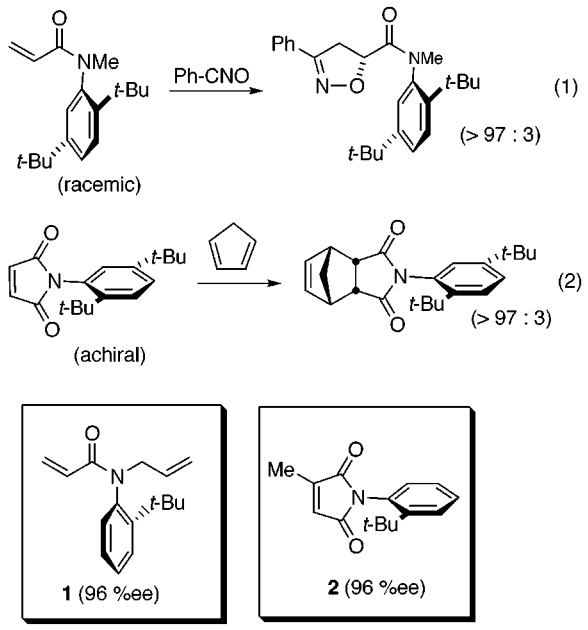
New axially chiral *N*-acryl-*N*-allyl-*o*-*tert*-butylanilide and *N*-(*o*-*tert*-butylphenyl)-2-methylmaleimide with high optical purity and definite absolute configurations were prepared from *o*-*tert*-butylaniline and (*S*)-*O*-acetyl lactic acid or (*R*)-2-methylsuccinic acid, respectively. Iodine- or Lewis acid-mediated asymmetric Diels−Alder reaction of these axially chiral compounds with various dienes proceeded with high *endo* and diastereofacial selectivity.

Introduction

In contrast to axially chiral biaryl compounds such as binaphthyl and biphenyl derivatives which are widely used as chiral ligands or chiral auxiliaries,[1] the application of nonbiaryl axially chiral compounds to asymmetric reactions has not been reported so far except for a few examples.[2] On the other hand, stereoselective reactions using axially chiral amides or axially twisted imide derivatives of their racemic or achiral forms have been recently reported by several groups.[3,4] In particular, highly diastereoselective reactions with axially chiral *N*-acryl-*o*-*tert*-butylanilide and axially twisted *N*-(*o*-*tert*-butylphenyl)-maleimide, which were disclosed by Curran,[4a] Kishikawa,[4b] and Simpkins,[4c] should be noted as a new method for stereocontrol (Scheme 1). Curran termed such transfer of axial chirality into the newly constructed chiral center as "atropselective reaction".[4a] However, in these reactions, the racemic axially chiral anilides and *σ*-symmetrical maleimides which cannot be applied to an asymmetric reaction were used. Although Shimpkins et al. attempted to prepare an optical active anilide through the kinetic resolution of racemic *N*-propionyl-*o*-*tert*-butylanilide by a chiral lithium amide, the chiral anilide with insufficient optical purity (88% ee) was obtained in poor yield at the stage of about 90% conversion.[4c] In addition, there has been no report regarding determination of the absolute configuration of this anilide.

Scheme 1



In this paper, we report a synthesis of chiral *N*-acryl-*N*-allyl-*o*-*tert*-butylanilide **1** and *N*-(*o*-*tert*-butylphenyl)-2-methylmaleimide **2** with high optical purity (96% ee) and definite absolute configuration.[5] Furthermore, as an application to asymmetric reaction, the iodine- or Lewis acid-mediated Diels−Alder reaction of the axially chiral compounds which proceeds with high *endo* and diastereofacial selectivity is also described.

Results and Discussion

Synthesis of Optically Active Axially Chiral *N*-Acryl-*N*-allyl-*o*-*tert*-butylanilide and *N*-*o*-*tert*-Butylphenyl 2-Methylmaleimide. To prepare axially chiral compounds with high optical purity and definite

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(1) (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvatori, P. *Synthesis* **1992**, 503. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Fuji, K.; Yang, X.; Tanaka, K., Asakawa, N.; Hao, X. *Tetrahedron Lett.* **1996**, *37*, 7373 and references therein.

(2) (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694. (b) Kawamoto, T.; Taga, T.; Bessho, K.; Yoneda, F. Hayami, J. *Tetrahedron Lett.* **1994**, *35*, 8631. (c) Ohno, A.; Kunimoto, J.; Kawai, Y.; Kawamoto, T.; Tomishima, M.; Yoneda, F. *J. Org. Chem.* **1996**, *61*, 9344.

(3) (a) Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahadron Lett.* **1995**, *36*, 9219. (b) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899. (c) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2561. (d) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949 and references therein.

(4) (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (b) Kishikawa, K.; Tsuru, I.; Kohomoto, S.; Yamamoto, M.; Yamada, K. *Chem. Lett.* **1994**, 1605. (c) Hughes, A. D.; Price, D. A.; Shishkin, O.; Shimpkins, N. S. *Tetrahadron Lett.* **1996**, *37*, 7607.

(5) Preliminary communication of this work: Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447.

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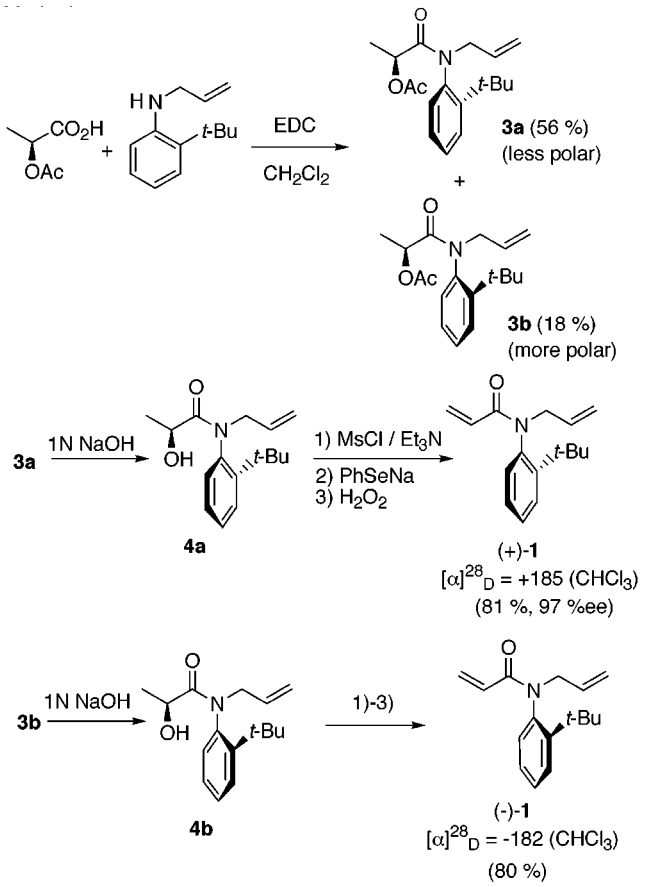
Scheme 2



absolute configuration, the optical resolution based on the formation of diastereomeric derivatives with certain optically active compounds was investigated. After a survey of various optically active compounds, the resolution through the formation of a carboxamide **3** from *N*-allyl-*o*-*tert*-butylaniline and (*S*)-*O*-acetyl lactic acid[6] was found to be the most effective. These diastereomeric anilides **3a** and **3b** on the basis of the axial chirality of the *o*-*tert*-butylanilide moeity and the chiral α-carbon of lactic acid can be easily separated by column chromatography [TLC (SiO_2), $\Delta R_f = 0.13$, hexane/AcOEt = 3], readily affording a diastereomerically pure anilide (Scheme 2). In this condensation reaction, although various methods such as the use of DCC, $(EtO)_2P(O)CN$, $(PhO)_2P(O)N_3$, and mixed anhydride were attempted, anilide **3** could not be obtained in good yield (≤20%) because of the low reactivity of the aniline having a bulky *tert*-butyl group at the ortho position.[7] On the other hand, it was found that the use of 2 equiv of lactic acid and 3-ethyl-1-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC) as a condensation reagent and a highly concentrated solution (1.5 M) were required to get products **3** in good yield. Under these conditions, **3a** and **3b** were obtained in 74% yield in a ratio of 3:1.

The stereochemistries of these anilides **3a** and **3b** were determined on the basis of X-ray crystallography of **3b**. The X-ray crystal structure indicates that the planes of the amide and aryl group are twisted by 83° (Figure 1).

(6) (*S*)-*O*-Acetyl lactic acid was purchased from Kanto Chemicals Co.

(7) Although anilides **3a** and **3b** were obtained in quantitative yield from *N*-allyl-*o*-*tert*-butyl aniline and (*S*)-acetoxypropionyl chloride (commercially available), the preparation through this method gave **1** with lower optical purity (82% ee).

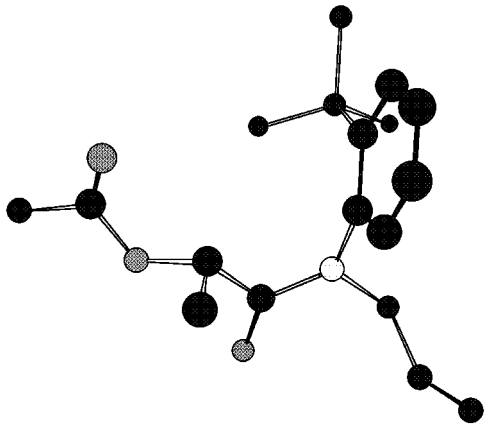
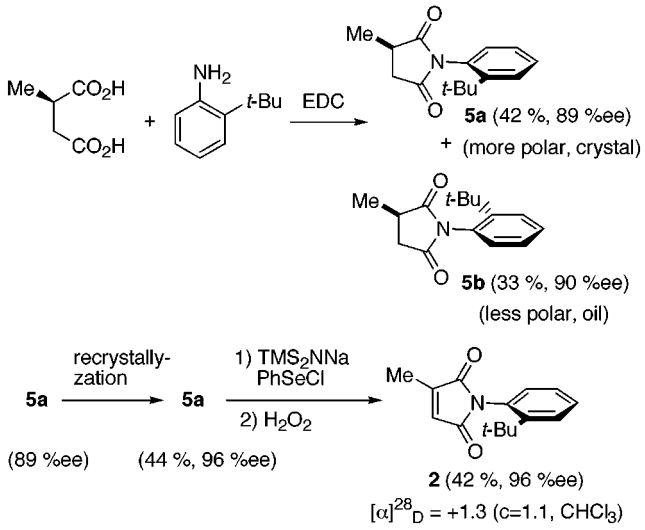


Figure 1. Chem 3D drawing of **3b** obtained by X-ray analysis. Hydrogen atoms have been omitted for clarity.

Scheme 3



Anilides **3a** and **3b** were converted to the corresponding *N*-acryl anilides (+)-**1** and (−)-**1** in good yields in accordance with Scheme 2, respectively. The physical data of (+)-**1** completely coincided with those of (−)-**1** except for the sign of $[\alpha]_D$. The ee of (+)-**1** having $[\alpha]_D$ = +185 ($CHCl_3$) was estimated to be 97% by HPLC analysis using a CHIRALPAK AS column.

Axially twisted *N*-(*o*-*tert*-butylphenyl)-maleimides reported by Curran and Kishikawa are achiral compounds with a symmetrical plane;[4a,b] therefore, we tried to prepare a chiral α-monosubstituted *N*-(*o*-*tert*-butylphenyl)-maleimide in optically active form.

The condensation reaction of (*R*)-2-methylsuccinic acid[8] with *o*-*tert*-butylaniline proceeded to give a good yield (75%) of diastereomer mixture of succinimides in a ratio of **5a**:**5b** = 1.3:1 (Scheme 3). Similar to the case of anilide **3**, the use of EDC as a condensation reagent and a highly concentrated solution (3 M) were required to get good yield of product **5**. These diastereomeric imides **5a** (crystal) and **5b** (oil) can be easily separated by column chromatography [TLC (SiO_2), $\Delta R_f = 0.04$, hexane/AcOEt = 3] to give diastereomerically pure imides. However, the ee of the separated imides **5a** and **5b** was estimated to be 89% and 90%, respectively, by HPLC analysis using a CHIRALPAK OJ column (**5a**: 30% *i*-PrOH in hexane,

(8) (*R*)-2-Methylsuccinic acid was purchased from Azmax Co. Ltd.

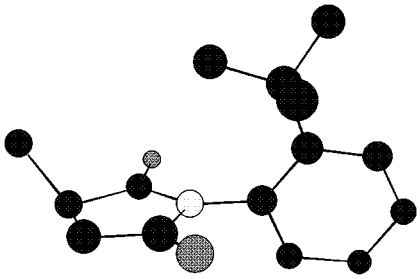
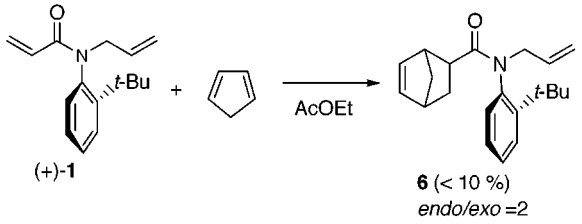


Figure 2. Chem 3D drawing of **5a** obtained by X-ray analysis. Hydrogen atoms have been omitted for clarity.

Scheme 4



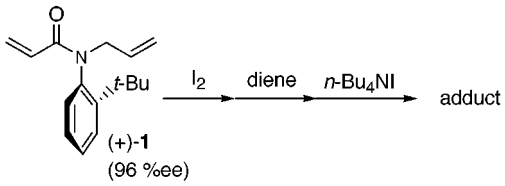
5b: 30% *i*-PrOH in hexane); thus, this condensation reaction was accompanied with partial epimerization. The optical purity of **5a** could be improved by recrystallization from hexane−AcOEt (10:1); that is, **5a** of 96% ee was obtained in 44% yield.

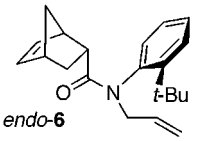
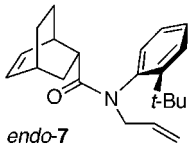
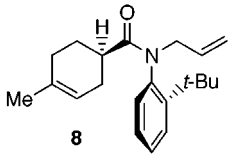
The stereochemistries of these imides **5a** and **5b** were determined on the basis of X-ray crystallography of **5a**. The X-ray crystal structure indicates that the plane of the aryl group is almost perpendicular to the plane of the cyclic imide moiety (85°, Figure 2). As shown in Scheme 3, **5a** could be converted to maleimide **2** in 42% yield without racemization. The ee of (+)-**2** having $[\alpha]^{28}_{D} = +1.3$ was estimated to be 96% by HPLC analysis using a CHIRALPAK AD column.

Regarding the racemization of these axially chiral compounds, at 80 °C, the half-lives of **1** and **2** were estimated to be 33 and 15 h, respectively. The optical purity of anilide **1** did not change after standing for more than one month at room temperature, while imide **2** racemized slowly at room temperature. For example, the optical purity of **2** (96% ee) dropped to 82% ee after 4 weeks at room temperature. The racemization of **2** could be prevented by storing in a freezer; that is, no racemization of **2** was observed after 8 weeks at −20 °C. Thus, use of **1** and **2** as chiral reagents for asymmetric reactions should be possible.

Application to Asymmetric Diels−Alder Reaction. For the investigation of the efficacy of anilide **1** and imide **2** as chiral reagents, asymmetric Diels−Alder reactions using **1** and **2** were examined. It has been pointed out that enamide derivatives compared to enals and enoates sometime work less well with a diene even in the presence of Lewis acid.[9,10] Indeed, the reaction of anilide (+)-**1** with cyclopentadiene at room temperature for 2 d afforded Diels−Alder adduct **6** in low yield (<10%, Scheme 4). In addition, in this case, diastereomer mixtures which may correspond to *endo*- or *exo*-isomers were obtained in a ratio of 2:1.

Table 1. Iodine-Mediated Asymmetric Diels−Alder Reaction of (+)-1[a]



Entry	Diene	Major Product	Yield (%)[b]	diastereomer ratio[c]
1		 endo-**6**	92	*endo/exo* = 30 *endo*-**6** (29/1)
2		 endo-**7**	84	*endo/exo* > 50 *endo*-**7** (14/1)
3		 **8**	87	20 : 1

[a] Diels-Alder Reaction: **1** (1 mmol), I_2 and diene (2 mmol), AcOEt (5 mL), -78°C - rt. [b] Isolated yields. [c] The ratios were determined on the basis of 300 MHz ^{1}HNMR.

We have recently found that in the presence of I_2, the Diels−Alder reaction of *N*-allylic enamide proceeds in good yield through an activating process involving the formation of a cationic iodocyclization intermediate.[10,11] The application of the iodine-mediated activating method to the asymmetric Diels−Alder reaction[12] of anilide (+)-**1** resulted in remarkable improvement in the reactivity and the selectivity (Table 1). The reaction of anilide (+)-**1** with cyclopentadiene in the presence of I_2 proceeded in good yield (92%) even at below room temperature to give the adduct **6** with high *endo* and diastereofacial selectivity (29:1:1, entry 1). The reaction with cyclohexadiene also gave the adduct **7** in good yield (84%) with almost complete *endo* selectivity and high diastereofacial selectivity (14:1, entry 2). In the reaction of an unreactive diene such as isoprene, the adduct **8** was also obtained in good yield (87%) with high diastereoselectivity (20:1, entry 3).

The relative and absolute configurations of major products *endo*-**6** and *endo*-**7** were determined based on the comparison of the ^{1}H NMR and the $[\alpha]_D$ values after conversion to the known alcohols **9**[13] and **10**[14] by $LiAlH_4$ reduction,[15] respectively, while that of **8** was determined

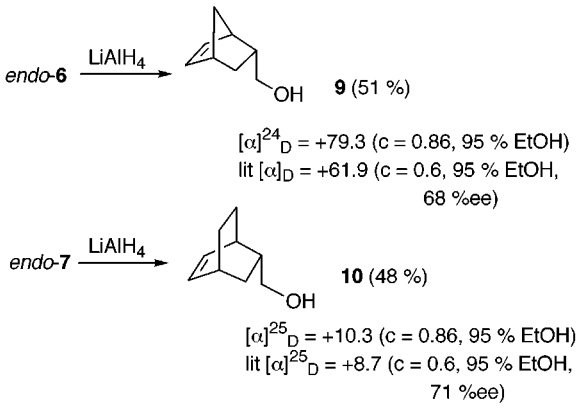
(9) (a) Jung, M.; Vaccaro, W.; Buszek, K. *Tetrahedron Lett.* **1989**, *30*, 1893. (b) Nakagawa, M.; Lai, Z.; Torisawa, Y.; Hino, T. *Heterocycles* **1990**, *31*, 999.

(10) Kitagawa, O.; Aoki, K.; Inoue, T.; Taguchi, T. *Tetrahadron Lett.* **1995**, *36*, 593.

(11) We have also found α-iodination reaction of unsaturated carboxamides and *N*-allylic enamides derivatives through a similar iodine-mediated activating process. (a) Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahadron Lett.* **1992**, *33*, 1299. (b) Kitagawa, O.; Kikuchi, N.; Hanano, T.; Aoki, K.; Yamazaki, T.; Okada, M.; Taguchi, T. *J. Org. Chem.* **1995**, *60*, 7161.

(12) Reviews in relation to asymmetric Diels−Alder reactions using a chiral auxiliary; (a) Paquette, L. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 455. (b) Helmchen, G.; Karge, R.; Weetman, J. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: New York, 1986; Vol. 4, p 262. (c) Oppolzer, W. *In Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press, Inc.: New York, 1991; Vol. 5, p 315. (d) Ishizuka, T.; Kunieda, T. *Rev. Heteroat. Chem.* **1996**, *15*, 227.

Scheme 5



by X-ray crystallography. In all cases shown in Table 1, it was found by HPLC analysis of products using a chiral column that the reactions proceed without loss of the optically purity.

The observed high reactivity and diastereoselectivity can be rationalized based on the structure of cationic iodocyclization intermediate **1A** (Scheme 6). ^{1}H NMR spectrum data of **1A** obtained by reaction of **1** with I_2 in $CDCl_3$ indicated marked downfield shifts of olefinic hydrogens, demonstrating significant decrease in electron density of the olefinic moeity as compared with **1**. In this spectrum, two sets of signals which may be due to the diastereomer on the basis of axial chirality and the newly constructed asymmetric center were observed in a ratio of 2.9:1. On the other hand, although the conformation between the olefin and the iminium moeity (*s-trans* or *s-cis*) could not be determined by NOE experiment, it was tentatively assigned to be *s-trans* based on the chemical shifts of olefinic protons (H_a, H_b) in intermediates **1A** and previously reported **11A**[10] derived from *N*-allyl *N*-benzyl acrylamide, and the *s-trans* structure of the latter **11A** was determined by NOE experiment. That is, because of anisotropy effect by a Ph group perpendicular to an imidate plane in *s-trans* conformer of **1A**, the α-hydrogen H_a may appear at a more upfield site than that in **11A**, while in *s-cis* confomer of **1A**, the chemical shift of *β*-hydrogen H_b should considerably differ from that of H_b in **11A**. In ^{1}H NMR of **1A** observed, H_a appeared at an upfield site (6.13 ppm) in comparison with that (6.93 ppm) of **11A**, while the chemical shift of H_b is similar to that of H_b in **11A**. Thus, the diene should preferentially attack from the opposite side of the *tert*-Bu group in *s-trans* intermediate **1A** to give products with high diastereoselectivity.

The conformation of **1A** assumed from ^{1}H NMR was also supported by MM and semiempirical PM3 calucu-lations; that is, in the most stable conformer of *trans*-**1A** having *s-trans* orientation estimated by calculation, the plane of the aryl group is almost perpendicular to that of the iminium part (93°), and the conformation between the olefin and the iminium part is antiperiplanar (158°, Figure 3).[16] In this conformer, the iodine atom of the iodomethyl group is located outside of the five-membered ring remote from the olefin part; thus, the diastereofacial selectivity may be considerably controlled by the *tert*-Bu group but not by the iodomethyl group. In addition, the *s-trans* confomer having the lowest energy level was also found to be more stable than the corresponding *s-cis* conformer by 2.1 kcal/mol by PM3 calculation (Figure 4). The energy difference between *s-trans* and *s-cis* conformers corresponds to a population ratio of 97:3 at 300 K.

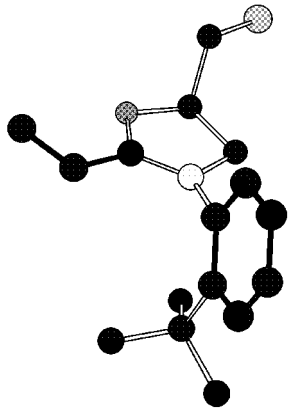
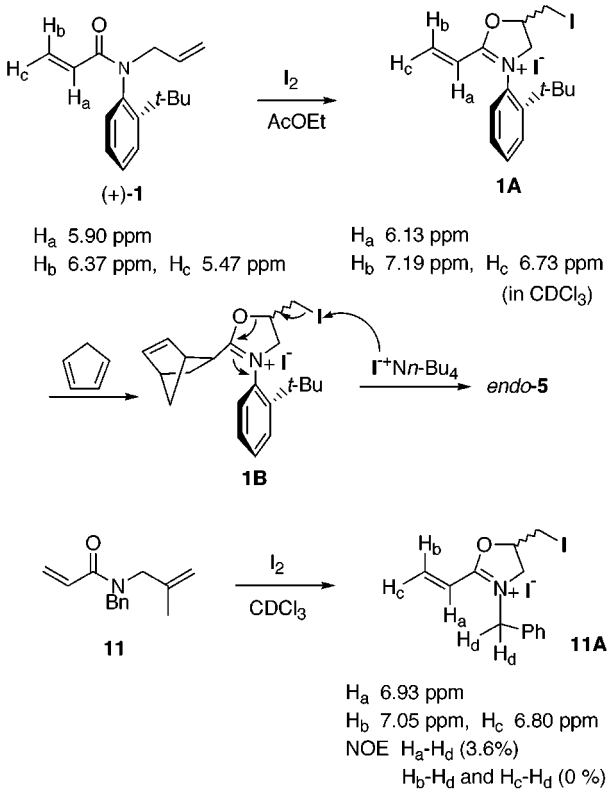


Figure 3. The most stable confomer of *trans*-**1A** (*s-trans*) estimated by MM and MD calculation.

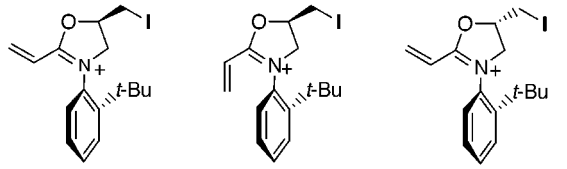
Scheme 6



The conclusions regarding the conformation of intermediate **1A** on the basis of the ^{1}H NMR analysis and the MO calculation cannot be extrapolated to analysis of the reactive rotamer in transition-state rationalizations of the asymmetric Diels−Alder reaction according to the

(13) Janssen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 5513.
(14) Arai, Y.; Takadoi, M.; Koizumi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4162.
(15) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343.

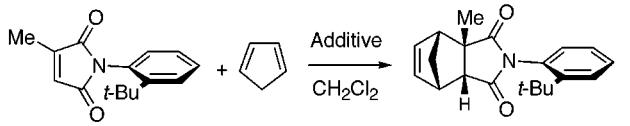
(16) The conformation of **1A** was preexamined through MM and MD calculations using MM2 force field as implemented in MacroModel 4.5 (Department of Chemistry, Columbia University, New York). Molecular dynamics calculation in vacuo at 300 K was carried out with a path length of 100 ps and followed by minimizing random structures sampled after multiple 1 ps intervals. Final full geometry was then optimized by semiempirical PM3 calculation as implemented in SPARTAN 4.0 (Wave function Inc., California).



trans-**1A** (s-*trans*) (172.8 kcal/mol) *trans*-**1A** (s-*cis*) (174.9 kcal/mol) *cis*-**1A** (s-*trans*) (173.5 kcal/mol)

Figure 4. Standard heats of formation of **1A** estimated by PM3 calculation.

Scheme 7



(+)-**2** (96 %ee) **12** (> 97 : 3, 96 %ee)

Additive	Conditions	Yield
none	rt, 3 d	83 %
Et_2AlCl	rt, 20 min	quantitative

Curtin−Hammett principle.[17] Neverthless, these results are in agreement with the diastereoselectivities which were observed in the present reaction. On the other hand, although the stereochemistries of diastereomers of **1A** observed in ^{1}H NMR are not clear, the observed ratio (2.9:1) was quite close to that (3.1:1) estimated from standard heats of formation of *trans*- and *cis*-**1A** (Figure 4).

In the Diels−Alder reaction of maleimide (+)-**2** with cyclopentadiene, although prolonged reaction time (3 days) was required at room temperature, the reaction proceeded in good yield (83%) even in the absence of activating reagents (Scheme 7). In the presence of Et_2-AlCl, the reaction was completed within 20 min at room temperature to give the adduct **12** in a quantitative yield.[18] In these reactions, almost complete *endo* and diastereofacial selectivities were observed as determined by 300 MHz ^{1}H NMR. The structure of the adduct **12** confirmed by X-ray analysis indicates that the attack of the diene to **2** occurs in an *endo*-mode from the opposite side of the *tert*-Bu group (see Supporting Information).

In conclusion, we have succeeded in the synthesis of chiral *N*-acryl-*N*-allyl-*o*-*tert*-butylanilide and *N*-(*o*-*tert*-butylphenyl)-2-methylmaleimide with high optical purity and definite absolute configuration. In addition to the stability of these axially chiral compounds which can be stored without racemization at an appropriate temperature, the above highly diastereoselective Diels−Alder reaction should indicate the usefulness of these compounds as chiral reagents.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400- and 300-MHz spectrometer. In ^{1}H and ^{13}C NMR spectra, chemical shifts were 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). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm i.d. prepacked column (silica gel, 50 μm) with a UV detector.

(*S*)-*N*-Allyl-*N*-(2-*tert*-butylphenyl)-2-acetoxypropionamide (3a and 3b). To a solution of (*S*)-*O*-acetyl lactic acid (4 g, 30 mmol) and *N*-allyl-*o*-*tert*-butylaniline (2.8 g, 15 mmol) in CH_2Cl_2 (8 mL) was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) (5.8 g, 30 mmol) at room temperature. After being stirred for 15 h, the mixture was poured into water and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 9) gave **3a** (less polar, 2.58 g, 56%) and **3b** (more polar, 0.82 g, 18%). **3a**: colorless solid; mp 44 °C; $[\alpha]^{25}_D = +55.0$ ($c = 1.0$, $CHCl_3$); IR (KBr) 2971, 1745, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, $J = 6.4$ Hz), 1.38 (s, 9H), 1.98 (3H, s), 3.36 (1H, dd, $J = 8.1$, 14.1 Hz), 4.95 (1H, tdd, $J = 1.5$, 4.9, 14.1 Hz), 5.02 (1H, q, $J = 6.4$ Hz), 5.11 (1H, md, $J = 17.0$ Hz), 5.18 (1H, dd, $J = 0.8$, 10.2 Hz), 5.99 (1H, dddd, $J = 4.9$, 8.1, 10.2, 17.0 Hz), 7.06 (1H, dd, $J = 1.6$, 7.8 Hz), 7.15 (1H, dt, $J = 1.5$, 7.8 Hz), 7.32 (1H, ddd, $J = 1.5$, 7.2, 7.8 Hz), 7.56 (1H, dd, $J = 1.6$, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.7, 20.8, 32.2, 36.1, 54.7, 67.6, 118.9, 126.3, 128.9, 130.1, 131.9, 137.9, 146.0, 169.2, 169.4; MS (*m*/*z*) 304 ($M^+ + 1$), 288. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.35; H, 8.30; N, 4.56. **3b**: colorless crystals; mp 94−95 °C; $[\alpha]^{25}_D = -99.0$ ($c = 1.0$, $CHCl_3$); IR (KBr) 2967, 1738, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, $J = 6.5$ Hz), 1.35 (s, 9H), 2.02 (3H, s), 3.34 (1H, dd, $J = 8.2$, 14.1 Hz), 4.95 (1H, tdd, $J = 1.3$, 5.0, 14.1 Hz), 5.08 (1H, q, $J = 6.5$ Hz), 5.09 (1H, md, $J = 17.1$ Hz), 5.18 (1H, d, $J = 10.4$ Hz), 5.98 (1H, m), 6.92 (1H, dd, $J = 1.5$, 7.8 Hz), 7.19 (1H, dt, $J = 1.4$, 7.4 Hz), 7.34 (1H, dt, $J = 1.5$, 7.4 Hz), 7.58 (1H, dd, $J = 1.5$, 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 17.8, 20.9, 31.9, 36.1, 54.4, 67.7, 119.1, 126.5, 128.9, 130.4, 131.5, 131.9, 137.8, 146.4, 169.7, 169.8; MS (*m*/*z*) 304 ($M^+ + 1$), 288. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.25; H, 8.30; N, 4.42. In ^{1}H and ^{13}C NMR spectra of **3a** and **3b**, the minor signals which may be due to the existence of the amide C−N rotamers were also observed in a ratio of 20:1 and 10:1, respectively.

***N*-Acryl-*N*-allyl-2-*tert*-butylanilide [(+)-1].** To a mixture of 1 N NaOH (5 mL) and EtOH (2 mL) was added **3a** (1.15 g, 3.8 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was poured into water and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave **4a** (993 mg, quantitative, see Supporting Information). To a solution of **4a** (993 mg, 3.8 mmol) and Et_3N (0.68 mL, 4.9 mmol) in THF (8 mL) was added methanesulfonyl chloride (0.38 mL, 4.9 mmol) at 0 °C. After being stirred for 30 min at room temperature, the mixture was poured into aqueous NH_4-Cl solution and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 7) gave the mesylate. To a solution of PhSeSePh (890 mg, 2.85 mmol) in EtOH (2 mL) was added $NaBH_4$ (216 mg, 5.7 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. To this was added the mesylate in EtOH (5 mL) at 0 °C, the whole was stirred for 4 h at room temperature, and then THF (2 mL) and 30% H_2O_2 (5 mL) were added to the mixture. After being stirred for 20 h at 0 °C to room temperature, the mixture was poured into aqueous $Na_2S_2O_3$ solution and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 20) gave (+)-**1** (754 mg, 3.1 mmol). The ee of (+)-**1** (97% ee) was determined by HPLC analysis using a CHIRALPAK AS column [25 cm × 0.46 cm i.d.; solvent, 0.1% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**1**; $t_R = 20.6$ min, (−)-**1**; $t_R = 15.5$ min]. (+)-**1**: colorless solid; mp 41−42 °C; $[\alpha]^{28}_D = +185.0$ (97% ee, $c = 1.1$, $CHCl_3$); IR (KBr) 2965, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (9H, s), 3.41 (1H, dd, $J = 8.1$, 14.1 Hz), 5.00 (1H, tdd, $J = 1.3$, 5.1, 14.1 Hz), 5.10 (1H, md, $J = 17.1$ Hz), 5.17 (1H, d, $J = 9.9$ Hz),

(17) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(18) In the presence of Et_2AlCl, the reaction of (+)-**2** with cyclohexadiene gave a complex mixture together with recovery of (+)-**2**.

5.47 (1H, dd, J = 2.1, 10.3 Hz), 5.90 (1H, dd, J = 10.3, 16.8 Hz), 6.03 (1H, dddd, J = 5.1, 8.1, 9.9, 17.1 Hz), 6.37 (1H, dd, J = 2.1, 16.8 Hz), 6.94 (1H, dd, J = 1.5, 7.8 Hz), 7.18 (1H, dt, J = 1.5, 7.4 Hz), 7.33 (1H, dt, J = 1.5, 7.3 Hz), 7.57 (1H, dd, J = 1.5, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 31.9, 35.7, 54.0, 118.5, 126.6, 127.2, 128.4, 128.7, 129.4, 131.9, 132.2, 139.0, 146.5, 165.3; MS (*m*/*z*) 243 (M^+), 228. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.06; H, 8.55; N, 5.61.

(*R*)-*N*-(2-*tert*-Butylphenyl)-2-methylsuccinimide (5a and 5b). To a solution of (*R*)-methylsuccinic acid (1.59 g, 12 mmol) and *o*-*tert*-butylaniline (1.56 mL, 10 mmol) in CH_2Cl_2 (4 mL) was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) (2.3 g, 12 mmol) under argon atmosphere at room temperature. After being stirred for 15 h, the mixture was poured into 2% HCl and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 7) gave **5b** (less polar, 810 mg, 33%) and **5a** (more polar, 1.03 g, 42%). The optical purity of **5a** (89% ee, 1.03 g) was improved to 96% ee (0.453 g, 44% yield) by recrystallization from hexane−AcOEt (30 mL-3 mL). **5a**: colorless solid; mp 103−106 °C; $[\alpha]^{26}_D$ = +9.9 (96% ee, *c* = 1.0, $CHCl_3$); IR (KBr) 2968, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.47 (3H, d, J = 7.2 Hz), 2.50 (1H, dd, J = 4.2, 17.3 Hz), 3.02 (1H, m), 3.09 (1H, dd, J = 9.2, 17.3 Hz), 6.84 (1H, dd, J = 1.5, 7.8 Hz), 7.29 (1H, dt, J = 1.4, 7.6 Hz), 7.39 (1H, dt, J = 1.5, 7.9 Hz), 7.58 (1H, dd, J = 1.4, 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 16.6, 31.6, 35.2, 35.6, 37.0, 127.3, 128.7, 129.6, 130.5, 130.6, 147.9, 176.7, 180.3; MS (*m*/*z*) 245 (M^+), 230. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.64; H, 7.76; N, 5.56. **5b**: colorless oil; $[\alpha]^{26}_D$ = +5.3 (90% ee, *c* = 1.05, $CHCl_3$); IR (KBr) 2986, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (9H, s), 1.46 (3H, d, J = 7.1 Hz), 2.51 (1H, dd, J = 4.3, 17.7 Hz), 3.02 (1H, m), 3.11 (1H, dd, J = 9.3, 17.7 Hz), 6.83 (1H, dd, J = 1.5, 7.8 Hz), 7.28 (1H, dt, J = 1.5, 7.6 Hz), 7.38 (1H, dt, J = 1.5, 7.6 Hz), 7.58 (1H, dd, J = 1.4, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 16.5, 31.5, 35.1, 35.5, 36.9, 127.3, 128.7, 129.7, 130.3, 130.6, 147.9, 176.5, 180.6; MS (*m*/*z*) 245 (M^+), 230. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.79; N, 5.47.

***N*-(2-*tert*-Butylphenyl)-2-methylmaleinimide [(+)-2].** To a solution of **5a** (313 mg, 1.28 mmol) in toluene (13 mL) was added TMS_2NNa (1 M THF solution, 1.28 mL, 1.28 mmol) at −78 °C. After being stirred for 10 min at −78 °C, PhSeCl (245 mg, 1.28 mmol) was added to the reaction mixture, and then the mixture was stirred for 1.5 h at −78 °C. The mixture was poured into 2% HCl and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. To the residue were added THF (5 mL) and 30% H_2O_2 (2 mL) at 0 °C, and then the mixture was stirred for 1.5 h at room temperature. The mixture was poured into 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 = 12) gave (+)-**2** (133 mg, 43%). The ee of (+)-**2** (96% ee) was determined by HPLC analysis using a CHIRALPAK AD column [25 cm × 0.46 cm i.d.; 1% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-**2**; t_R = 10.5 min, (+)-**2**; t_R = 11.9 min]. (+)-**2**: colorless oil; $[\alpha]_D$ = +1.3 (96% ee, *c*= 1.1, $CHCl_3$); IR (KBr) 2960, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (9H, s), 2.18 (3H, d, J = 1.9 Hz), 6.51 (1H, q, J = 1.9 Hz), 6.89 (1H, dd, J = 1.4, 7.7 Hz), 7.26 (1H, dt, J = 1.4, 7.7 Hz), 7.38 (1H, dt, J = 1.6, 8.1 Hz), 7.57 (1H, dd, J = 1.6, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 11.1, 31.5, 35.3, 127.1, 128.2, 128.4, 129.6, 129.7, 131.3, 146.6, 149.4, 170.8, 171.8; MS (*m*/*z*) 243 (M^+), 228. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.21; H, 6.89; N, 5.87.

General Procedure of Iodine-Mediated Diels−Alder Reaction. To a solution of (+)-**1** (96% ee, 243 mg, 1 mmol) in AcOEt (5 mL) was added I_2 (508 mg, 2 mmol) at room temperature. After being stirred for 30 min, cyclopentadiene (0.16 mL, 2 mmol) was added, and then the reaction mixture was stirred for 15 h at −78 °C to room temperature. *n*-Bu_4NI (739 mg, 2 mmol) was added to the mixture, and after being stirred for 2 h, the mixture was poured into aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with 2% HCl and brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 20) to give a mixture of major-*endo*-**6**, minor-*endo*-**6**, and *exo*-**6** (285 mg, 92%, major-*endo*-**6**/minor-*endo*-**6**/*exo*-**6** = 29/1/1). Further purification by MPLC (hexane/AcOEt = 12) gave major-*endo*-**6** (263 mg, 85%), minor-*endo*-**6** (3 mg, 1%), and *exo*-**6** (2 mg, 0.7%).

(*3R,4R,6R*), (*3R,4S,6R*), and (*3S,4S,6S*)-*N*-Allyl-*N*-(2-*tert*-butylphenyl)bicyclo[2.2.1]heptene-4-carboxamide [*endo*-6 (major), *exo*-6, *endo*-6 (minor)]. Major-*endo*-**6**: colorless solid; mp 65−66 °C; $[\alpha]^{22}_D$ = +243.9 (96% ee, *c* = 1.0, $CHCl_3$); IR (KBr) 2980, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (1H, d, J = 8.1 Hz), 1.21 (1H, ddd, J = 1.9, 4.3, 8.1 Hz), 1.36 (9H, s), 1.48 (1H, ddd, J = 2.5, 4.7, 11.3 Hz), 1.56−1.65 (1H, m), 2.61 (1H, ddd, J = 3.5, 4.7, 8.2 Hz), 2.77 (1H, brs), 2.83 (1H, brs), 3.26 (1H, dd, J = 8.2, 14.2 Hz), 4.90 (1H, tdd, J = 1.4, 4.8, 14.2 Hz), 5.06 (1H, qd, J = 1.1, 17.1 Hz), 5.14 (1H, d, J = 9.6 Hz), 5.89 (1H, dd, J = 3.0, 5.5 Hz), 5.97 (1H, dddd, J = 4.8, 8.2, 9.6, 17.1 Hz), 6.28 (1H, dd, J = 3.0, 5.5 Hz), 7.12 (1H, dd, J = 1.6, 7.7 Hz), 7.23 (1H, dt, J = 1.6, 7.2 Hz), 7.34 (1H, dt, J = 1.6, 7.2 Hz), 7.57 (1H, dd, J = 1.6, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 30.2, 32.2, 36.0, 42.0, 43.0, 46.8, 50.3, 54.2, 117.9, 126.4, 128.4, 129.6, 130.7, 132.1, 133.2, 137.2, 140.0, 146.2, 174.1; MS (*m*/*z*) 309 (M^+), 294. Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.41; H, 8.75; N, 4.41. Minor-*endo*-**6**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (1H, d, J = 8.2 Hz), 1.04 (1H, ddd, J = 2.4, 5.7, 11.2 Hz), 1.27 (1H, m), 1.41 (9H, s), 1.56 (1H, m), 2.59 (1H, ddd, J = 3.0, 5.6, 9.2 Hz), 2.71 (1H, brs), 2.92 (1H, brs), 3.27 (1H, dd, J = 8.2, 14.2 Hz), 4.91 (1H, tdd, J = 1.3, 5.0, 14.2 Hz), 5.01 (1H, dd, J = 1.1, 17.2 Hz), 5.09 (1H, d, J = 10.1 Hz), 5.92 (1H, dddd, J = 5.0, 8.2, 10.1, 17.2 Hz), 6.14 (1H, dd, J = 3.0, 5.5 Hz), 6.36 (1H, dd, J = 3.0, 5.5 Hz), 6.86 (1H, dd, J = 1.6, 7.6 Hz), 7.17 (1H, dt, J = 1.6, 7.6 Hz), 7.32 (1H, dt, J = 1.6, 7.2 Hz), 7.58 (1H, dd, J = 1.6, 7.2 Hz); MS (*m*/*z*) 309 (M^+), 294. *exo*-**6**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.01 (1H, ddd, J = 2.3, 8.3, 11.0 Hz), 1.24 (1H, d, J = 8.0 Hz), 1.33 (9H, s), 1.89 (1H, ddd, J = 1.0, 4.4, 8.1 Hz), 1.98−2.06 (2H, m), 2.74 (1H, brs), 2.89 (1H, brs), 3.34 (1H, dd, J = 8.2, 14.2 Hz), 4.96 (1H, tdd, J = 1.4, 4.8, 14.2 Hz), 5.08 (1H, qd, J = 1.6, 17.1 Hz), 5.16 (1H, d, J = 10.2 Hz), 5.70 (1H, dd, J = 3.0, 5.6 Hz), 5.96 (1H, dd, J = 3.0, 5.6 Hz), 6.03 (1H, dddd, J = 4.8, 8.2, 10.2, 17.1 Hz), 7.07 (1H, dd, J = 1.7, 7.6 Hz), 7.21 (1H, dt, J = 1.6, 7.6 Hz), 7.30 (1H, dt, J = 1.6, 7.2 Hz), 7.53 (1H, dd, J = 1.6, 7.2 Hz); MS (*m*/*z*) 309 (M^+), 294.

(4*R*)-Bicyclo[2.2.1]heptene-4-methanol (9). To a solution of *endo*-**6** (257 mg, 0.83 mmol) in THF (5 mL) was added $LiAlH_4$ (31.5 mg, 0.83 mmol) at 0 °C. After being stirred for 5 h at room temperature, the mixture was successively treated with AcOEt, H_2O, and 2% HCl and then extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (pentane/Et_2O = 5) gave **9** (53 mg, 51%). **9**: $[\alpha]^{24}_D$ = +79.3 (*c* = 0.86, 95% EtOH) [lit. $[\alpha]_D$ = +61.9 (68% ee, *c* = 0.6, 95% EtOH)]; ^{1}H NMR data coincided with that reported in the literature.[13]

Cationic Iodocyclization Intermediate (1A). To a solution of the anilide **1** (52 mg, 0.21 mmol) in $CDCl_3$ (8 mL) was added I_2 (161 mg, 0.63 mmol) at room temperature. After being stirred for 2 h, the ^{1}H NMR spectrum of the reaction mixture was measured. In ^{1}H NMR of **1A**, two sets of signals which may be due to the diastereomer on the basis of axial chirality and newly constructed asymmetric center were observed in a ratio of 2.9:1. Major-**1A**: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 4.02 (1H, dd, J = 3.0, 11.9 Hz), 4.11 (1H, dd, J = 4.9, 11.9 Hz), 4.48 (1H, dd, J = 9.1, 12.8 Hz), 5.14 (1H, dd, J = 9.8, 12.8 Hz), 5.84 (1H, m), 6.13 (1H, dd, J = 11.0, 17.2 Hz), 6.73 (1H, d, J = 11.0 Hz), 7.19 (1H, d, J = 17.2 Hz), 7.50−7.87 (4H, m). Minor-**1A**: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 3.81 (1H, dd, J = 6.4, 11.7 Hz), 3.86 (1H, dd, J = 4.6, 11.7 Hz), 4.58 (1H, dd, J = 8.2, 12.6 Hz), 5.03 (1H, dd, J = 10.5, 12.6 Hz), 5.84 (1H, m), 6.04−6.17 (2H, m), 6.73 (1H, d, J = 11.0 Hz), 7.19 (1H, d, J = 17.2 Hz), 7.50−7.87 (4H, m).

(1*S*,2*S*,6*R*,7*S*)-4-(2-*tert*-Butylphenyl)-2-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (12). To a solution of (+)-**2** (96% ee, 61 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) was added Et_2AlCl (0.95 M in hexane, 0.26 mL, 0.25 mmol) at room temperature. After being stirred for 10 min, cyclopentadiene (0.1 mL, 1.25 mmol) was added, and then the reaction mixture was stirred for 20 min at room temperature. The mixture was poured into 2% HCl solution and extracted with Et_2O. The Et_2O extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 12) to give **12** (77 mg, quantitative) as a single isomer. **12**: colorless solid; mp 162−164 °C; $[\alpha]^{26}_D$ = −35.0 (96% ee, c = 1.24, $CHCl_3$); IR (KBr) 2969, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (9H, s), 1.62 (3H, s), 1.81 (1H, td, J = 1.7, 9.2 Hz), 1.85 (1H, td, J = 1.5, 9.2 Hz), 2.98 (1H, d, J = 4.5 Hz), 3.03 (1H, m), 3.46 (1H, m), 6.30 (1H, dd, J = 3.0, 5.5 Hz), 6.39 (1H, dd, J = 3.0, 5.5 Hz), 6.72 (1H, dd, J = 1.5, 7.7 Hz), 7.22 (1H, dt, J = 1.5, 7.4 Hz), 7.36 (1H, dt, J = 1.6, 7.2 Hz), 7.52 (1H, dd, J = 1.5, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.3, 31.5, 35.5, 45.9, 50.3, 51.0, 51.6, 53.1, 127.2, 128.4, 129.5, 130.6, 131.1, 134.7, 136.8, 147.9, 177.9, 181.0; MS (*m*/*z*) 309 (M$^+$), 294. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.40; H, 7.44; N, 4.57.

Supporting Information Available: Characterization data and experimental procedures of **4a**, **4b**, *endo*-**7**, and **8**, and X-ray crystal data of **3b**, **5a, 8**, and **12** (95 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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