

Asymmetric Synthesis of Hydroisoquinoline Derivatives, a Key Intermediate for Manzamine Synthesis, by Diels–Alder Reaction Using 4-Amino-2-siloxybutadiene

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A novel method for the synthesis of chiral hydroisoquinolines by asymmetric Diels–Alder reaction of nitrogen-containing dienophiles and suitably protected aminosiloxybutadienes has been developed. The product could be a key intermediate for synthesis of manzamine alkaloids.

Hydroisoquinolines are widely found in the structures of biologically active natural and unnatural compounds **1**–**4** (Figure 1).[1–4] We have been studying the total synthesis of manzamine alkaloids **5** and **6** which were isolated from a marine sponge and have been shown to have a variety of interesting biological activities.[5,6] In 2003, we reported a synthesis of chiral hydroisoquinolines, a key intermediate for the synthesis of manzamine alkaloids, via Diels–Alder reaction (Scheme 1).[7]

The chiral dienophile **7**, which was prepared from L-serine, was reacted with TBS-protected Danishefsky diene **8** to give chiral hydroisoquinoline **9a** along with its diastereoisomer **9b**. Unfortunately, due to the high reaction temperature, the diastereoselectivity was low. Therefore, a new and more efficient synthetic route was required. We developed a new Diels–Alder route to construct the hydroisoquinoline skeleton **12** using dienophile **10** and aminosiloxybutadiene **11** in the presence of a chiral Lewis acid. In this paper, we report the details of this reaction (Scheme 2).[8]

A Diels–Alder reaction using highly reactive aminosiloxybutadienes was reported by Rawal and co-workers in 1997.[9a,9c] They also reported a diastereoselective version of this reaction using a chiral aminosiloxybutadiene[9b,9d] and finally developed a highly enantioselective Diels–Alder reaction in the presence of a catalytic amount of chiral Cr salen complex.[9f–9h] The aminosiloxybutadiene **11** has been reported to be highly

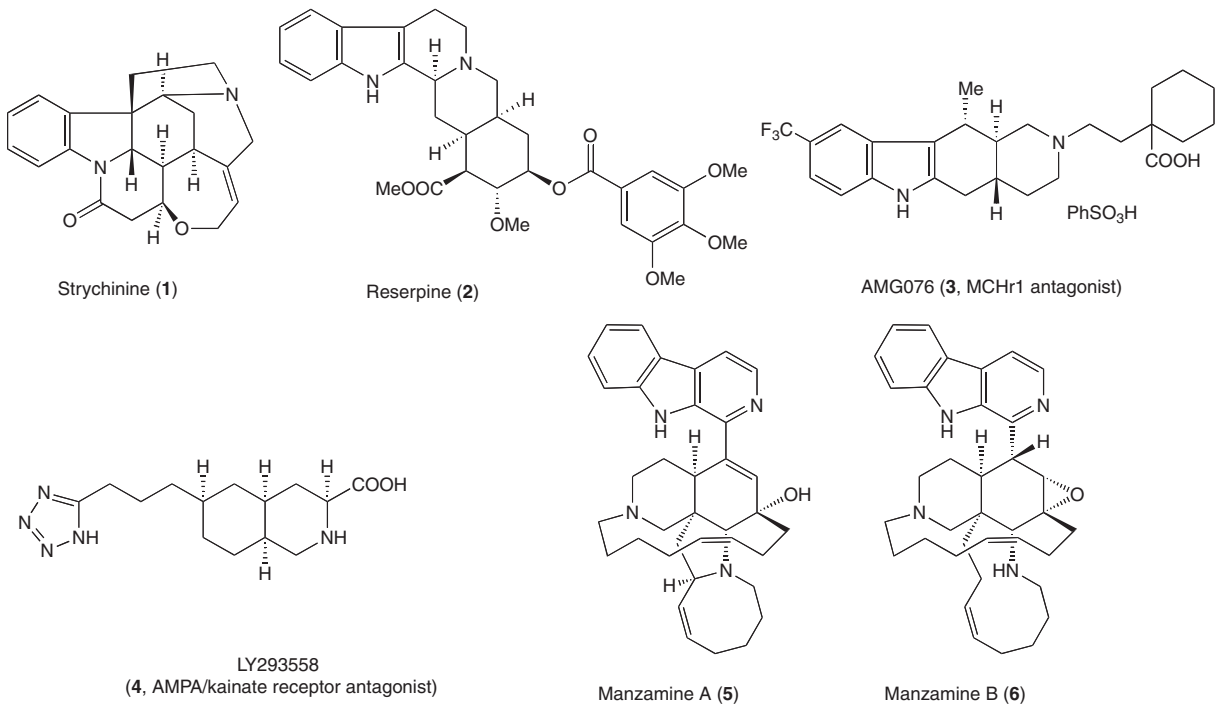

Figure 1. Natural and unnatural compounds with a hydroisoquinoline skeleton.

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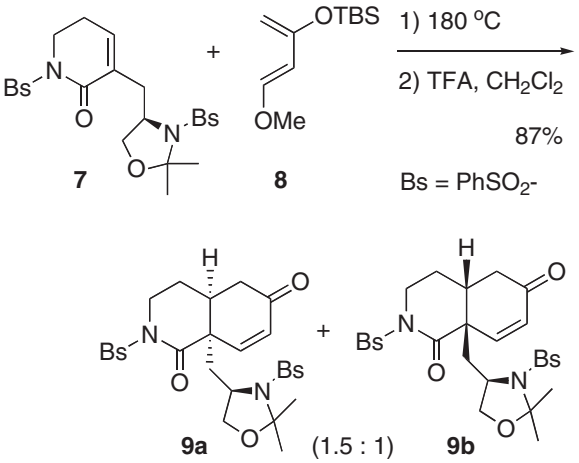
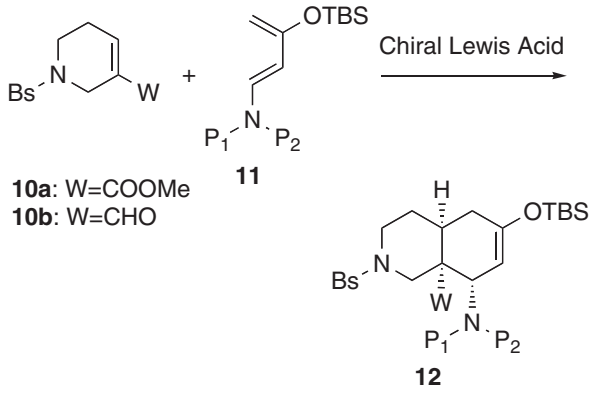
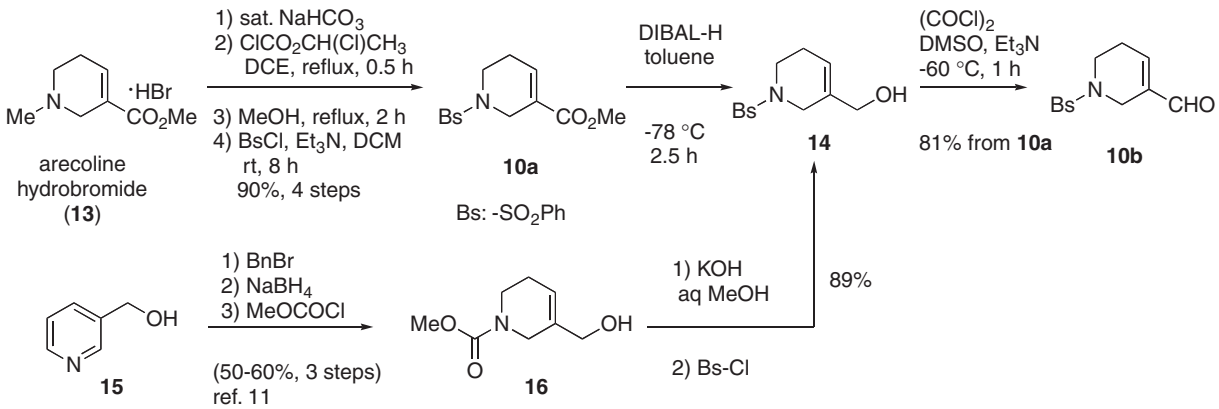


Scheme 1.



Scheme 2.



Scheme 3.

reactive in Diels–Alder reactions using an acyclic dienophile. However, examples that use a cyclic dienophile have been limited and the reactivity seems to be lower than that with an acyclic dienophile.[9e] Furthermore, no reaction using a nitrogen-containing heterocyclic dienophile has been reported, except for highly reactive maleimide.

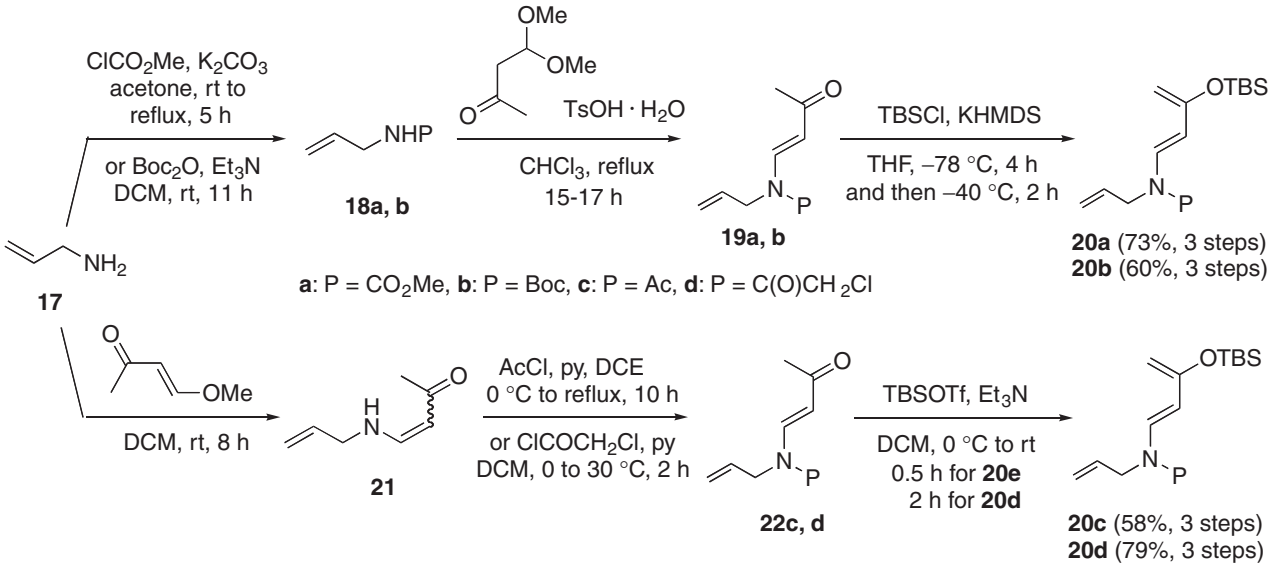
We first synthesized two dienophiles **10a** and **10b** which have a dehydropiperidine skeleton. A benzenesulfonyl (Bs) group was chosen as a protecting group because of its stability and feasibility for NMR analysis compared to an amide or carbamate group. Structurally related alkaloid arecoline **13**, which is commercially available as a hydrobromide, was demethylated by reacting it with 1-chloroethyl chloroformate.[10] The resulting carbamate was selectively removed and a secondary amino group was protected by a Bs group to give a dienophile **10a**. Reduction of the methyl ester by DIBAL followed by Swern oxidation gave the second dienophile **10b**. The alcohol **14** was also prepared from the inexpensive starting material **15** (Scheme 3).[11]

Four types of aminosiloxybutadienes **20a**–**20d** were then prepared. According to the procedure developed by Rawal,[9c] two carbamate dienes **20a** and **20b** were prepared as shown in Scheme 4. The same procedure was not successful for preparing amide dienes, and allylamine was first added to methoxybutenone. Enamine **21** was then converted to acetamide **22c** and chloroacetamide **22d**, which were then silylated with TBSOTf in the presence of triethylamine to give dienes **20c** and **20d**. These aminosiloxybutadienes are unstable on heating or treatment with acid and even on silica gel. They were prepared before use and purified by short alumina column chromatography.

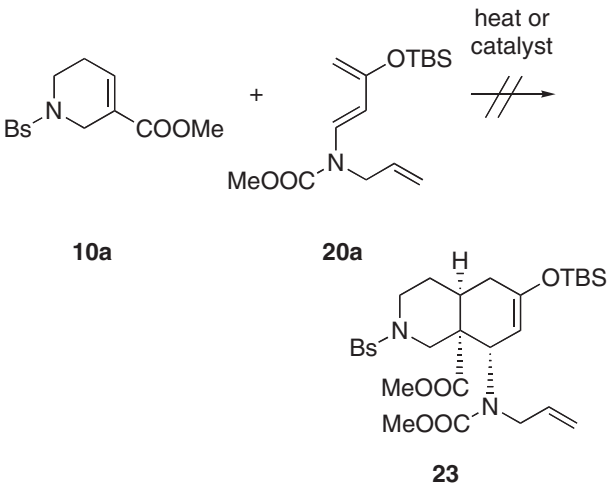
With dienes and dienophiles in hand, we began to study the Diels–Alder reaction of heterocyclic dienophile and aminosiloxybutadiene. However, the reaction between ester dienophile **10a** and carbamate diene **20a** did not proceed under a variety of thermal (up to 180 °C) and Lewis acid conditions ($EtAlCl_2$, $ZnCl_2$, and $Sc(OTf)_3$) (Scheme 5).

Fortunately, dienophile **10b** showed higher reactivity in the presence of Cr–salen complex **25**. However, 50 mol % of salen complex was required to promote the reaction between **20a** and **10b** to give adduct **24a** in 51% yield with 68% ee after 90 h at room temperature.[12] Among the four aminosiloxydienes **20**, the reaction using chloroacetamide **20d** proceeded faster and gave **24d** in 60% yield with 73% ee. Further optimization was carried out using a combination of **10b** and **20d** (Table 1).

The counter anion of the catalysts also affected the reactivity of the promoters (Table 2). The Cr–salen complexes **26**–**29** were prepared from **25** by an anion-exchange reaction as described in the literature,[9f,13,14] and their activities were tested. Among them, fluoride complex **29** was the most reactive promoter and **24d** was obtained in 75% yield with 95% ee (Entry 5). Even in the presence of Cr complex **29**, the reactions



Scheme 4.



Scheme 5.

using aminosiloxydienes **20a**–**20c** did not exceed the result obtained using **20d** (Entries 6–8).[15]

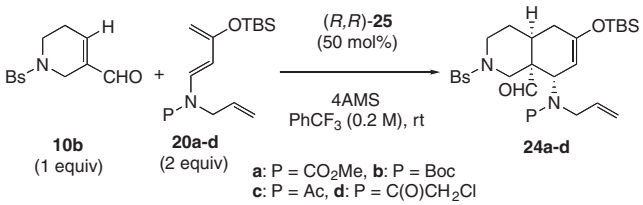
Although dienophile **10b** was more reactive than **10a**, smaller amounts of Cr complexes gave poor yields of the adduct (Table 3, Entries 1–4). A prolonged reaction time caused decomposition of the diene. The diene/dienophile molar ratio did not affect the product yield. Enantiomeric excess of the product reached 97% ee when the reaction was carried out at 0 °C. The reaction generally gave a single diastereomer in high enantiomeric excess. Further studies to indentify a more effective catalyst are underway.

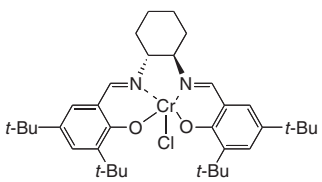
Enantiomerically pure **24d** was obtained by simple recrystallization from methanol. The relative and absolute stereochemistries of adduct **24d** were unambiguously determined by X-ray crystallographic analysis as shown in Figure 2. The product **24d** was determined to be an endo-adduct and all of the stereogenic centers had an S configuration, which corresponded to the stereochemistry of manzamines.

The observed high stereoselectivity could be explained by transition state models, which are the same as those proposed by Rawal (Figure 3).[9h] The aminosiloxydienes accessed activated dienophiles from the less-hindered side to avoid interaction with *t*-Bu groups and axial hydrogens in the cyclohexyl group.

Interestingly, aminosiloxydiene with a chloroacetyl group showed better reactivity than other dienes. Chloroacetaminodiene **20d** was 6 times more stable than carbamatedienes **20a**, as shown in Figure 4. When both **20a** and **20d** were treated with CD_3CO_2D in $CDCl_3$ and the decomposition rate was monitored by ^1H NMR, electron-rich carbamatediene **20a** decomposed faster. Generally, electron-rich dienes react faster

Table 1. Asymmetric Diels–Alder Reaction of Various Aminodienes Catalyzed by **25**



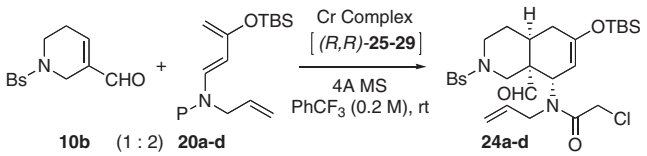


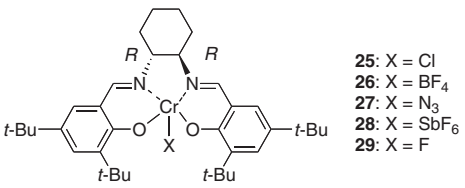
Cr(III)-Salen complex (**25**)

Entry	Diene	Time/h	Adduct	Yield/%	ee/%[a]
1	**20a**	90	**24a**	51	68
2	**20b**	90	**24b**	10	—
3	**20c**	55	**24c**	31	—
4	**20d**	31	**24d**	60	73

a) Enantiomeric excess was determined by HPLC analysis [Entry 1: DAICEL CHIRALCEL OD (hexane:*i*-PrOH = 95:5, flow rate: 1.0 mL min^{-1}, retention time: 17.8 and 21.0 min); Entry 4: DAICEL CHIRALCEL OD (hexane:*i*-PrOH = 95:5, flow rate: 1.0 mL min^{-1}, retention time: 23.8 and 28.6 min)].

Table 2. Effect of Cr Chiral Complex on the Asymmetric Diels–Alder Reaction of Aminosiloxydienes

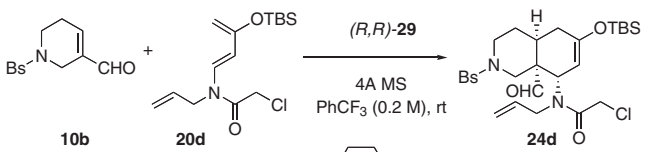


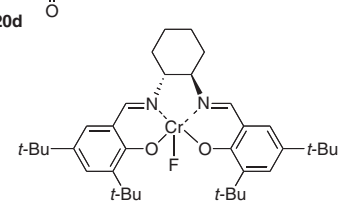


Cr(III)-Salen complex

Entry	Cr complex (mol %)	Diene	Time/h	Yield/%	ee/%
1	**25** (50)	**20d**	87	65	75
2	**26** (50)	**20d**	20	65	88
3	**27** (50)	**20d**	160	12	89
4	**28** (50)	**20d**	—	decomp.	—
5	**29** (50)	**20d**	20	75	95
6	**29** (50)	**20a**	72	70	92
7	**29** (50)	**20b**	282	58	—
8	**29** (50)	**20c**	42	57	—

Table 3. Optimization of the Asymmetric Diels–Alder Reaction of Aminosiloxydienes



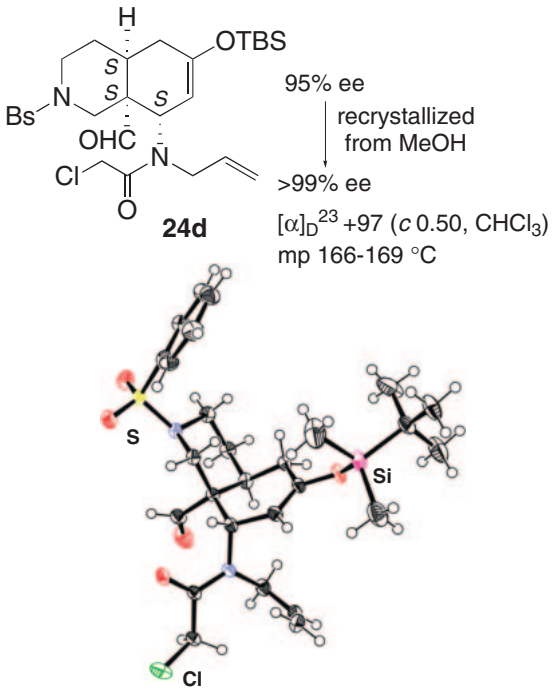


Cr(III)-Salen complex (**29**)

Entry	**29**/mol %	**10b**:**20d**	Time/h	Yield/%	ee/%
1	100	1:2	20	79	94
2	25	1:2	38	58	93
3	10	1:2	62	11	93
4	5	1:2	62	4	95
5	25	1:1	20	35	92
6	25	1:1.2	20	32	93
7	25	1:1.5	20	42	95
8	25	1.5:1	20	23	94
9	25	2:1	20	41	93
10[a)]	25	1:2	64	58	97

a) Reaction was performed at 0 °C.

with electron-deficient dienophiles in the Diels–Alder reaction because of favorable frontier orbital interaction. However, the more Lewis basic carbamate group in **20a** and **20b** or acetamino group in **20c** may interact with Cr complex and deactivate the promoter.



Structure of **24d** determined by X-ray analysis (Final R value 0.042, absolute structure paramater 0.06.)

Figure 2. Determination of relative and absolute stereochemistry.

Conclusion

We have established an effective method for synthesizing highly substituted chiral hydroisoquinoline derivatives by the asymmetric Diels–Alder reaction of a suitably protected aminosiloxydiene and a nitrogen-containing cyclic dienophile in the presence of Cr–salen complexes. A chloroacetyl protecting group for an amino moiety in dienes was essential for efficient conversion. A total synthesis of manzamine alkaloids using chiral hydroisoquinoline **24d** is under development.

Experimental

General. All reactions were carried under an argon atmosphere. Melting points were recorded on a Yanagimoto micro melting point apparatus, and are uncorrected. IR spectra were recorded on a JASCO FT/IR-230 spectrophotometer. ^{1}H NMR spectra were taken on 400 or 600 MHz instruments (JEOL JMN-GSX 400a, JEOL JMN-ECP 600) in the indicated solvent at rt unless otherwise stated. ^{13}C NMR spectra were taken at 100 or 150 MHz in the indicated solvent. HPLC analyses were performed on SHIMADZU LC-2010C, and Daicel chiral column (CHIRALCEL OD, Daicel Chemical Ind., Ltd.). Analytical TLC was carried on Merck Japan Limited Silica gel 60 F_{254} plates, and on Merck DC-Platten Aluminiumoxid 60 F_{254} plates. Preparative TLC was carried on Merck Silica gel 60 F_{254} plates. Silica gel column chromatography was performed using Silica gel PSQ-60B (Fuji Silysia Chemical Ltd.). Alumina column chromatography was performed using Merck Aluminiumoxid 90 aktivbasisch. MS spectrometries were performed on JEOL JMS-AX500 (LRFABMS), JEOL JMS-AX505 (LRFABMS), and JEOL JMS-HX110 (HRFABMS). Elemental and X-ray crystallographic analy-

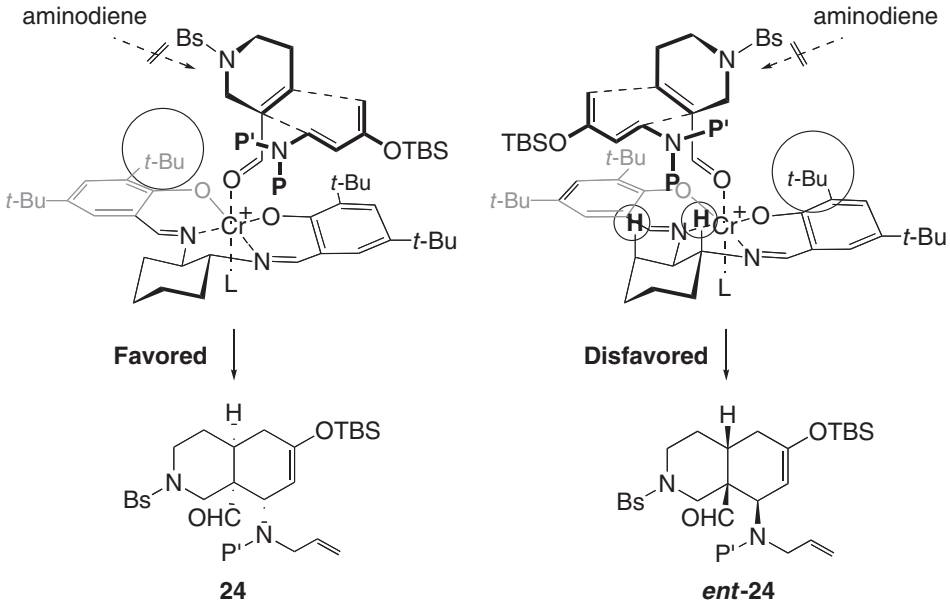
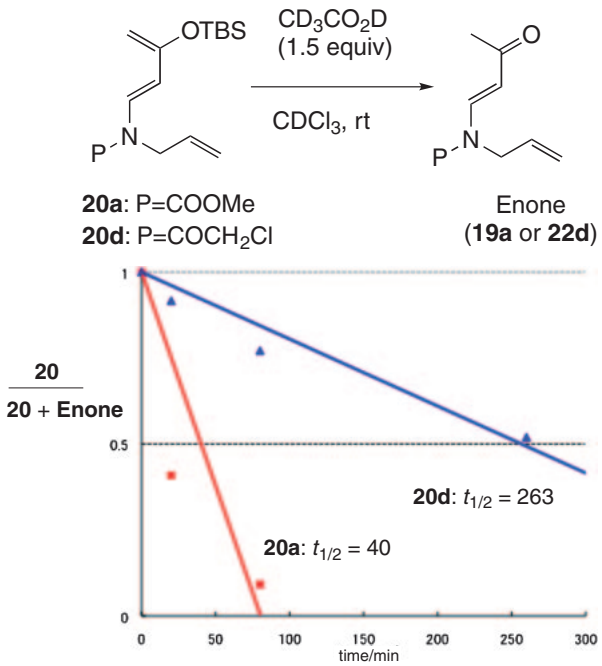


Figure 3. Plausible transition state in the Diels–Alder reaction.



time /min	20 / (20 + Enone)[a] 20a	20d
0	1.000	1.000
20	0.409	0.916
80	0.092	0.771
260	-	0.519

[a]calculated by ^{1}H-NMR

Figure 4. Decomposition experiments with **20a** and **20d**.

ses were carried out at The Chemical Analysis Center of Chiba University. Anhydrous solvents [tetrahydrofuran (THF), dichloromethane (DCM), and toluene] were used as received from Kanto Kagaku, Ltd. Other solvents and all commercially available reagents (Aldrich, TCI, Kanto Kagaku, Wako, Kishida, and Across) were purified by standard methods. Diene **20a** was prepared according literature procedure.[9c]

Methyl 1-Benzenesulfonyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10a). Arecoline hydrobromide (**13**) (25 g, 106 mmol) was dissolved in sat. $NaHCO_3$, and the resulting mixture was extracted with DCM several times. Combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in 1,2-dichloroethane (106 mL), and $ClCO_2CH(Cl)CH_3$ (12.6 mL, 116 mmol) was added dropwise over 10 min to the solution at 0 °C. The reaction mixture was then heated under reflux conditions for 30 min, and the solvent was concentrated in vacuo. The residue was dissolved in MeOH (159 mL), and the solution was heated under reflux conditions for 2 h. The mixture was cooled to rt, and the solvent was removed in vacuo.

To a solution of the residue in DCM (353 mL) were added Et_3N (37 mL, 265 mmol) and BsCl (15 mL, 117 mmol) at 0 °C. After being stirred for 8 h at rt, H_2O was added. The organic layer was separated and the aqueous layer was extracted with DCM twice. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in *n*-hexane) to afford **10a** as a colorless solid (26.9 g, 90%, 4 steps): mp 78–82 °C (*n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (tdt, $J = 5.9$, 4.1, 3.9 Hz, 2H), 3.20 (t, $J = 5.8$ Hz, 2H), 3.74 (s, 3H), 3.82 (td, $J = 2.7$, 2.2 Hz, 2H), 7.00 (tt, $J = 4.1$, 2.0 Hz, 1H), 7.55 (t like, $J = 7.3$ Hz, 2H), 7.61 (t like, $J = 7.3$ Hz, 1H), 7.83 (d like, $J = 7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.7, 41.7, 43.9, 51.8, 126.8, 127.5, 129.1, 132.9, 136.1, 137.3, 165.1; IR (KBr): ν 1716, 1458, 1446, 1420, 1389, 1342, 1313, 1299, 1272, 1234, 1201, 1172, 1108, 1050, 1007, 969, 903, 776, 742, 717, 689, 669, 581, 559 cm^{-1}; LRMS (FAB) m/z 282 $[M + H]^+$; HRMS (FAB) calcd for $C_{13}H_{16}NO_4S$ $[M + H]^+$ 282.0800, found 282.0794.

(1-Benzenesulfonyl-1,2,5,6-tetrahydropyridin-3-yl)methanol (14). To a solution of **10a** (27.9 g, 99.0 mmol) in toluene (198 mL) was added dropwise a solution of DIBAL-H in toluene (1.0 M, 198 mL, 198 mmol) over 30 min at −78 °C. After being stirred for 2.5 h, the reaction mixture was quenched by addition of sat. Rochelle's salt. The mixture was warmed to rt and stirred for 12 h at rt. The organic layer was separated, and the aqueous layer was

extracted with EtOAc twice. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in *n*-hexane) to afford **14** as a colorless oil (24.4 g, 97%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.46 (brs, 1H), 2.24 (m, 2H), 3.18 (t, $J = 5.7$ Hz, 2H), 3.62 (td, $J = 2.4$, 2.4 Hz, 2H), 4.03 (brs, 2H), 5.75 (m, 1H), 7.52–7.63 (m, 3H), 7.80–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.7, 42.6, 45.1, 64.7, 121.2, 127.5, 129.0, 132.7, 133.8, 135.9; IR (KBr): ν 3390, 3312, 3058, 2923, 2899, 2853, 1465, 1446, 1334, 1249, 1171, 1154, 1097, 1064, 1044, 998, 953, 914, 811, 746, 690, 589, 562 cm^{-1}; LRMS (FAB) m/z 254 $[M + H]^+$; HRMS (FAB) calcd for $C_{12}H_{16}NO_3S$ $[M + H]^+$ 254.0851, found 254.0844.

Alternative Synthesis of 14 from 16. A mixture of methyl carbamate **16**[11] (39.2 g, 0.229 mol) in methanol (190 mL) and a solution of KOH (50 g, 0.916 mol) in water (190 mL) was stirred at reflux for 18 h. The reaction mixture was then cooled to 0 °C with an ice bath and to it was added $NaHCO_3$ (38.5 g, 0.458 mol) and benzenesulfonyl chloride (80.9 g, 0.458 mol). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 4 h. Methanol was removed in vacuo and the remaining aqueous solution was extracted with Et_2O. Combined organic layers were washed with sat. aq NaCl, and then dried over $MgSO_4$. After solvent was evaporated, the residue was chromatographed on silica gel, eluting with EtOAc:hexane (2:3) to give **14** (51.5 g, 89%) as a colorless oil.

1-Benzenesulfonyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde (10b). To a solution of $(COCl)_2$ (11.8 mL, 135 mmol) in DCM (550 mL) was added dropwise a solution of DMSO (19.2 mL, 270 mmol) in DCM (100 mL) over 30 min at −60 °C. After being stirred for 10 min, a solution of **14** (28.5 g, 113 mmol) in DCM (200 mL) was added. The reaction mixture was stirred for 0.5 h, and then Et_3N (63 mL, 450 mmol) was added. After addition of H_2O at rt, the organic layer was separated and the aqueous layer was extracted with DCM twice. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from EtOAc/*n*-hexane to afford **10b** as colorless crystals (23.0 g, 81%): mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.54–2.59 (m, 2H), 3.27 (t, $J = 5.6$ Hz, 2H), 3.81 (td, $J = 2.3$, 2.2 Hz, 2H), 6.81 (tt, $J = 4.0$, 1.7 Hz, 1H), 7.52 (t like, $J = 7.3$ Hz, 2H), 7.59 (t like, $J = 7.3$ Hz, 1H), 7.81 (d like, $J = 7.1$ Hz, 2H), 9.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.4, 42.2, 42.4, 127.6, 129.2, 133.0, 135.9, 137.6, 147.0, 191.1; IR (KBr): ν 3071, 2942, 2897, 2833, 1680, 1650, 1467, 1444, 1416, 1397, 1341, 1293, 1239, 1204, 1167, 1095, 1000, 963, 920, 865, 833, 757, 743, 718, 688, 575, 556 cm^{-1}; LRMS (FAB) m/z 252 $[M + H]^+$; HRMS (FAB) calcd for $C_{12}H_{14}NO_3S$ $[M + H]^+$ 252.0694, found 252.0688.

***N*-Allyl-*N*-[(*E*)-3-oxo-1-butenyl]acetamide (22c).** To a solution of allylamine (**17**) (7.8 g, 0.13 mol) in DCM (270 mL) was added 4-methoxy-3-butene-2-one (13.3 g, 0.13 mol) at 0 °C. After being stirred for 8 h at rt, the reaction mixture was slowly concentrated in vacuo. This crude enamine (**21**, a volatile oil) was used for the next reaction without further purification.

To a solution of the crude enamine in DCE (266 mL), were added pyridine (22 mL, 0.27 mol) and acetyl chloride (11.4 mL, 0.88 mol) at 0 °C. The solution was stirred for 1 h at 0 °C, and then heated under reflux conditions for 9 h. After cooling to rt, H_2O was added. The organic layer was separated and aqueous layer was extracted with DCM twice. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in *n*-hexane) to afford enamine **22c** as a yellow oil (18.2 g, 82%, 2 steps): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 2.23 (s, 3H), 2.34 (s, 3H), 4.26–4.27 (m, 2H), 5.13 (ddd, $J = 17.2$, 2.0, 0.8 Hz, 1H), 5.22 (d, $J = 10.4$ Hz, 1H), 5.67 (d, $J = 14.4$ Hz, 1H), 5.75 (ddt, $J = 17.2$, 10.4, 5.2 Hz, 1H), 8.06 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ 21.8, 28.3, 46.1, 109.3, 117.4, 130.7, 140.7, 170.1, 196.7; IR (neat): ν 3508, 1683, 1615, 1584, 1391, 1264, 1214, 948 cm^{-1}; LRMS (FAB) m/z 168 $[M + H]^+$; HRMS (FAB) calcd for $C_9H_{14}NO_2$ $[M + H]^+$ 168.1025, found 168.1039.

***N*-Allyl-*N*-[(*E*)-3-oxo-1-butenyl]chloroacetamide (22d).** To a solution of allylamine (**17**) (50 g, 0.88 mol) in DCM (880 mL) was added 4-methoxy-3-butene-2-one (87.7 g, 0.88 mol) at 0 °C. After being stirred for 8 h at rt, the reaction mixture was slowly concentrated in vacuo. To a solution of the resulting crude enamine in DCM (1760 mL) was added pyridine (78 mL, 0.96 mol) and chloroacetyl chloride (70 mL, 0.88 mol) at 0 °C. The reaction mixture was stirred for 1 h, and then heated to 30 °C for an additional 1 h. After cooling to rt, H_2O was added. The organic layer was separated and the aqueous layer was extracted with DCM twice. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 20% EtOAc in *n*-hexane) to afford enamine **22d** as a yellow oil (176 g, quant, 2 steps): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 2.25 (s, 3H), 4.29 (s, 2H), 4.31 (ddd, $J = 4.9$, 1.7, 1.7 Hz, 2H), 5.17 (d, $J = 17.3$ Hz, 1H), 5.26 (d, $J = 10.5$ Hz, 1H), 5.76 (d, $J = 13.9$ Hz, 1H), 5.77 (ddt, $J = 17.1$, 10.3, 5.1 Hz, 1H), 8.01 (d, $J = 13.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ 28.0, 40.8, 46.4, 110.9, 117.6, 130.1, 139.6, 166.1, 196.3; IR (KBr): ν 3372, 3087, 2991, 2949, 2251, 1683, 1621, 1587, 1397, 1357, 1328, 1286, 1262, 1222, 1174, 1128, 1006, 947, 800, 734, 685 cm^{-1}; LRMS (FAB) m/z 202 $[M + H]^+$; HRMS (FAB) calcd for $C_9H_{13}ClNO_2$ $[M + H]^+$ 202.0635, found 202.0633.

***t*-Butyl Allyl[(*E*)-3-(*t*-butyldimethylsiloxy)-1,3-butadienyl]-carbamide (20b).** Diene **20b** was prepared by Rawal's protocol.[9c] To a solution of **17** (1.0 g, 17.5 mmol) in DCM (90 mL) were added Boc_2O (4.2 g, 19.3 mmol) and Et_3N (4.9 mL, 35 mmol) at rt. After being stirred for 11 h, the solvent was removed in vacuo. The residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to afford *t*-butyl *N*-allylcarbamate (**18b**)[16] (2.55 g, 93%).

To a stirring solution of *t*-butyl allylcarbamate (**18b**) (2.55 g, 16.2 mmol) in $CHCl_3$ (50 mL) were added acetylacetaldehyde dimethylacetal (6.64 g, 50.3 mmol) and $TsOH \cdot H_2O$ (255 mg, 1.34 mmol). The reaction mixture was heated under reflux condition for 15 h, and concentrated in vacuo. The residue was purified by flash column chromatography (25% EtOAc in *n*-hexane) to afford *t*-butyl allyl[(*E*)-3-oxo-1-butenyl]carbamate (**19b**)[17] (1.85 g, 51%).

To a solution of *t*-butyl allyl[(*E*)-3-oxo-1-butenyl]carbamate (**19b**) (4.0 g, 17.8 mmol) in THF (60 mL), was added TBSCl (4.89 g, 26.7 mmol). The reaction mixture was cooled to −78 °C, and to it a 1.0 M solution of KHMDS in THF (23.1 mL, 23.1 mmol) was added dropwise over 30 min. The solution was slowly warmed to −40 °C, and stirred for 2 h. The red solution was diluted with Et_2O and filtered through a Celite pad. The filtrate was concentrated in vacuo to give a crude product which was purified by alumina column chromatography (0 to 10% EtOAc in *n*-hexane) to afford **20b** (4.61 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.19 (s, 6H), 0.97 (s, 9H), 1.48 (s, 9H), 4.10 (s, 2H), 4.15 (br, 2H), 5.09–5.15 (m, 2H), 5.31 (d, $J = 14.0$ Hz, 1H), 5.71–5.81 (m, 1H), 7.37 (d, $J = 14.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ

−4.7, 18.2, 25.9, 28.3, 46.2, 47.7, 91.8, 106.9, 114.1, 116.1, 128.7, 132.4, 152.6; IR (neat): ν 3384, 3115, 2957, 2930, 2858, 1715, 1648, 1590, 1472, 1462, 1391, 1368, 1299, 1252, 1216, 1163, 1025, 1005, 942, 879, 828, 781 cm^{-1}.

***N*-Allyl-*N*-[(*E*)-3-(*t*-butyldimethylsiloxy)-1,3-butadienyl]acetamide (20c).** To a solution of enamine **22c** (2.9 g, 17 mmol) in DCM (43 mL) was added Et_3N (3.6 mL, 19 mmol). The reaction mixture was cooled to 0 °C, and TBSOTf (4.3 mL, 19 mmol) was added dropwise. After being stirred for 0.5 h, the reaction was quenched by addition of cold sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM twice. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by alumina column chromatography (0% to 20% EtOAc in *n*-hexane) to afford **20c** as a yellow oil (3.4 g, 71%): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 0.20 (s, 6H), 0.98 (s, 9H), 2.22 (s, 3H), 4.19 (overlapped d (J = 6.8 Hz) and brs, 2.5H), 4.27 (brs, 1.5H), 5.10–5.17 (m, 2H), 5.49 (d, J = 14.0 Hz, 1H), 5.75 (m, 1H), 7.13 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ −4.7, 21.9, 25.8, 45.1, 53.3, 93.2, 109.6, 116.5, 128.7, 132.3, 154.1, 169.1; IR (neat): ν 3450, 2956, 2930, 2858, 1682, 1644, 1400, 1300, 1216, 1024, 828 cm^{-1}.

***N*-Allyl-*N*-[(*E*)-3-(*t*-butyldimethylsiloxy)-1,3-butadienyl]chloroacetamide (20d).** To a solution of enamine **22d** (19 g, 95 mmol) in DCM (240 mL) was added Et_3N (17 mL, 123 mmol). The reaction mixture was cooled to 0 °C, and TBSOTf (25 g, 95 mmol) was added dropwise. After being stirred for 2 h, the reaction was quenched by addition of cold sat. $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with DCM twice. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by alumina column chromatography (0% to 20% EtOAc in *n*-hexane) to afford aminodiene **20d** as a yellow oil (23.7 g, 79%): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 0.23 (s, 6H), 1.00 (s, 9H), 4.15–4.32 (overlapped, 6H), 5.16 (d, J = 17.6 Hz, 1H), 5.20 (d, J = 12.0 Hz, 1H), 5.62 (d, J = 13.6 Hz, 1H), 5.78 (ddd, J = 17.6, 12.0, 4.8 Hz, 1H), 7.13 (d, J = 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ −4.7, 18.2, 25.8, 40.9, 46.1, 94.3, 111.8, 117.0, 127.2, 131.3, 153.5, 165.2; IR (neat): ν 3448, 3087, 2955, 2930, 2886, 2858, 1678, 1644, 1589, 1471, 1463, 1440, 1408, 1362, 1306, 1255, 1218, 1194, 1134, 1021, 1005, 941, 924, 840, 809, 782, 738, 690, 570, 543 cm^{-1}; LRMS (FAB) m/z 316 $[M + H]^+$; HRMS (FAB) calcd for $C_{15}H_{27}ClNO_2Si$ $[M + H]^+$ 316.1500, found 316.1487.

General Procedure for the Asymmetric Diels–Alder Reaction (1 mmol Scale Experiments). After a mixture of Cr–salen complex (**25**–**29**, 50 mol %, based on dienophile) and oven-dried powdered 4A MS (0.8 g) was dried under vacuum for 20 min, a solution of dienophile **10b** (1 mmol) in $PhCF_3$ (5 mL) was added and the mixture was stirred for 1 h at rt. To this mixture, was added aminodiene **20** (2 mmol) and the resulting mixture was stirred at rt. The reaction mixture was then filtered through a pad of Celite and the pad was washed with DCM. The filtrate was concentrated in vacuo and residue was purified by flash column chromatography (20 to 50% EtOAc in *n*-hexane) to afford **24** as a colorless foam.

Methyl (4a*S*,8*S*,8a*S*)-Allyl[2-benzenesulfonyl-6-(*t*-butyldimethylsiloxy)-8a-formyl-1,2,3,4,4a,5,8,8a-octahydroisoquinolin-8-yl]carbamate (24a) and Methyl (4a*S*,8*S*,8a*S*)-Allyl(2-benzenesulfonyl-8a-formyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-8-yl)carbamate: Because of instability, the structure analysis of **24a** was limited. NMR spectra showed that **24a** was a mixture of rotational isomers due to the carbamate group. ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.51 (brs, 1H), 1.78–1.84 (overlapped, 2H), 2.25 (d, J = 12.0 Hz, 1H), 2.36 (brs, 1H), 2.87 (brs, 2H), 3.10 (brs, 1H), 3.48 (brs, 1H), 3.66 (s, 3H), 3.81 (br, 2H), 4.66 (br, 1H), 4.72 (br, 1H), 5.27 (m, 2H), 5.73 (broad, 1H), 7.4–7.5 (m, 3H), 7.77–7.79 (m, 2H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ −4.5, −4.4, 14.2, 17.9, 21.0, 29.7, 47.1, 52.9, 55.0, 60.4, 63.7, 116.1, 127.8, 129.2, 133.1, 135.0, 135.3, 171.2, 201.9; IR (neat): ν 2954, 2927, 2858, 1693, 1446, 1257, 1171 cm^{-1}; LRMS (FAB) m/z 549 $[M + H]^+$; HRMS (FAB) calcd for $C_{27}H_{41}N_2O_6SSi$ $[M + H]^+$ 549.2455, found 549.2448.

Its structure was further determined after conversion to methyl (4a*S*,8*S*,8a*S*)-allyl(2-benzenesulfonyl-8a-formyl-6-oxo-1,2,3,4,4a,4,5,6,7,8,8a-decahydroisoquinolin-8-yl)carbamate by cleavage of silylether. To a solution of **24a** (28 mg, 51 mmol) in DCM (1.5 mL) was added CSA (5.9 mg, 25 mmol). After being stirred at rt for 4 h, the reaction was quenched by addition of sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM twice. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in *n*-hexane) to afford methyl (4a*S*,8*S*,8a*S*)-allyl(2-benzenesulfonyl-8a-formyl-6-oxo-1,2,3,4,4a,4,5,6,7,8,8a-decahydroisoquinolin-8-yl)carbamate as a colorless oil (20 mg, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 1.61–1.67 (overlapped, 2H), 2.00 (br, 1H), 2.12–2.19 (overlapped br and d (J = 15.7 Hz), 2H), 2.39 (br, 1H), 2.49 (dd, J = 15.0, 3.3 Hz, 1H), 3.07 (dd, J = 15.0, 5.5 Hz, 1H), 3.70 (s, 5H), 3.82 (dd, J = 15.7, 8.1 Hz, 1H), 4.01 (br, 2H), 4.48 (br, 1H), 5.23 (d, J = 10.3 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.74–5.84 (m, 1H), 7.57–7.60 (m, 2H), 7.64–7.68 (m, 1H), 7.77–7.80 (m, 2H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ 27.9, 35.3, 42.8, 43.4, 46.1, 47.6, 51.3, 52.8, 53.9, 55.7, 118.7, 128.0, 129.3, 133.3, 133.4, 135.1, 156.6, 198.7, 206.1; IR (neat): ν 3067, 2928, 2852, 2852, 1684, 1658, 1629 cm^{-1}; LRMS (FAB) m/z 435 $[M + H]^+$; HRMS (FAB) calcd for $C_{21}H_{27}N_2O_6S$ $[M + H]^+$ 435.1590, found 435.1578.

***t*-Butyl (4a*S*,8*S*,8a*S*)-Allyl[2-benzenesulfonyl-6-(*t*-butyldimethylsiloxy)-8a-formyl-1,2,3,4,4a,5,8,8a-octahydroisoquinolin-8-yl]carbamate (24b):** ^{1}H NMR (C_6D_6, 400 MHz, 75 °C): δ 0.03 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.12 (br, 1H), 1.25–1.31 (br, 1H), 1.34 (s, 9H), 1.55–1.67 (m, 1H), 2.03 (br, 2H), 2.74 (br, 2H), 3.12 (br, 1H), 3.34 (br, 1H), 3.97 (br, 2H), 4.73 (s, 1H), 4.76 (s, 1H), 5.01 (d, J = 10.3 Hz, 1H), 5.16 (d, J = 17.3 Hz, 1H), 5.78–5.88 (m, 1H), 6.95–7.03 (m, 3H), 7.61–7.64 (m, 2H), 9.95 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz, 75 °C): δ −4.32, −4.27, 18.1, 25.8, 27.2, 28.4, 30.0, 30.8, 43.3, 47.9, 49.9, 52.5, 55.4, 59.9, 103.2, 115.8, 129.0, 132.6, 136.2, 137.0, 150.9, 155.6, 169.8, 200.8; IR (neat): ν 3418, 3060, 2956, 2931, 2858, 1732, 1682, 1471, 1463, 1446, 1393, 1367, 1335, 1266, 1254, 1210, 1170, 1092, 978, 931, 889, 837, 781, 740, 692 cm^{-1}; LRMS (FAB) m/z 592 $[M + H]^+$; HRMS (FAB) calcd for $C_{30}H_{47}N_2O_6SSi$ $[M + H]^+$ 591.2917, found 591.2892.

(4a*S*,8*S*,8a*S*)-*N*-Allyl-*N*-[2-benzenesulfonyl-6-(*t*-butyldimethylsiloxy)-8a-formyl-1,2,3,4,4a,5,8,8a-octahydroisoquinolin-8-yl]-acetamide (24c): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.26–1.27 (m, 1H), 1.37–1.40 (m, 1H), 1.79–1.88 (overlapped, 2H), 1.98 (s, 3H), 2.11–2.14 (m, 1H), 2.45 (m, 1H), 2.63 (m, 1H), 3.27–3.32 (m, 1H), 3.80 (m, 1H), 3.86 (s, 2H), 4.62 (d, J = 4.8 Hz, 1H), 4.96 (s, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.8 Hz, 1H), 5.67–5.77 (m, 1H), 7.51–7.61 (m, 3H), 7.76–7.78 (m, 2H), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C): δ −4.5, −4.4, 14.1, 17.9, 20.9, 22.5,

25.5, 26.6, 29.6, 47.1, 52.6, 53.5, 60.2, 101.0, 116.4, 127.8, 129.1, 132.9, 135.0, 136.0, 170.9, 172.2, 202.0; IR (KBr): ν 2930, 1723, 1637, 1355, 1171, 1092, 838, 751, 692, 577 cm^{-1}; LRMS (FAB) m/z 533 $[M + H]^+$; HRMS (FAB) calcd for $C_{27}H_{41}N_2O_5SSi$ $[M + H]^+$ 533.2505, found 533.2494.

(4a*S*,8*S*,8a*S*)-*N*-Allyl-*N*-[2-benzenesulfonyl-(*t*-butyldimethylsiloxy)-8a-formyl-1,2,3,4,4a,5,8,8a-octahydroisoquinolin-8-yl]-chloroacetamide (24d): Mp 166–169 °C (MeOH); $[\alpha]_D^{23}$ +97 (*c* 0.50, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz, 75 °C): δ 0.04 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.09–1.14 (br, 1H), 1.38 (br, 1H), 1.59 (dd, $J = 18.1$, 6.8 Hz, 1H), 1.89 (br, 1H), 2.07 (dd, $J = 17.6$, 5.9 Hz, 1H), 2.69 (br, 1H), 2.77 (br, 1H), 3.14 (br, 1H), 3.35 (br, 1H), 3.69 (br, 2H), 3.77 (ddd, $J = 17.6$, 2.2, 2.2 Hz, 1H), 3.89–3.97 (m, 1H), 4.65 (d, $J = 3.7$ Hz, 1H), 4.85 (d, $J = 3.7$ Hz, 1H), 4.93 (dd, $J = 10.5$, 1.0 Hz 1H), 5.01 (d, $J = 17.3$ Hz, 1H), 5.50–5.59 (m, 1H), 6.98–7.03 (m, 3H), 7.64–7.66 (m, 2H), 9.85 (s, 1H); ^{13}C NMR (C_6D_6, 400 MHz, 75 °C): δ −4.31, −4.28, 18.1, 25.8, 27.3, 31.1, 42.0, 43.4, 47.9, 52.4, 55.1, 102.2, 117.2, 128.1, 129.1, 132.6, 134.9, 137.0, 151.3, 167.7, 200.1; IR (KBr): ν 3449, 2931, 2857, 1719, 1655, 1473, 1458, 1447, 1419, 1354, 1254, 1208, 1170, 1092, 977, 940, 878, 837, 782, 749, 691, 669, 578, 419 cm^{-1}; LRMS (FAB) m/z 567 $[M + H]^+$; HRMS (FAB) calcd for $C_{27}H_{40}ClN_2O_5SSi$ $[M + H]^+$ 567.2116, found 567.2079; Anal. Calcd for $C_{27}H_{39}ClN_2O_5SSi$: C, 57.17; H, 6.93; N, 4.94%. Found: C, 57.21; H, 6.97; N, 4.90%.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-734357 for compound No. **24d**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail:deposit@ccdc.cam.ac.uk).

A Large Scale Synthesis of 24d (68 mmol Scale Reaction). A 500-mL round bottom flask was charged with (*R*,*R*)-salen–Cr complex **29** (21.1 g, 34.2 mmol, 50 mol %; based on dienophile **20d**) and oven-dried powdered 4A MS (34.2 g, 500 mg $mmol^{-1}$). Then the flask was flushed with argon. To this mixture was added a solution of dienophile **10b** (17.2 g, 68.4 mmol) in CF_3Ph (300 mL), and the resulting mixture was stirred for 1 h at rt. Diene **20d** (43.2 g, 137 mmol) in CF_3Ph (40 mL) was added to the reaction mixture via a cannula. After being stirred for 20 h at rt, the reaction mixture was filtered though a Celite pad and the pad was washed with CH_2Cl_2. Combined filtrates were concentrated in vacuo. The residue was chromatographed on silica gel, eluting with EtOAc:*n*-hexane (4:1) to give **24d** which was solidified by trituration with EtOAc:*n*-hexane (1:4). The solids were filtered and washed with EtOAc:*n*-hexane (1:4) to give **24d** (26.0 g, 67%, 99% ee) as a colorless solid. Enantiomeric purity of **24d** was determined to >99% ee by HPLC using a chiral column (DAISEL CHIRALCEL OD, hexane:*i*-PrOH = 95:5, flow rate: 1.0 mL min^{-1}, retention time of **24d** and *ent*-**24d**, 30.1 and 35.6 min.).

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15 The reaction of **10a** with **20d** under the optimized conditions in the presence of Cr complex **29** was unsuccessful and the decomposition of **20d** was observed.

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