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Investigation of Lewis Acid-Catalyzed Asymmetric Aza-Diels−Alder Reactions of 2*H*-Azirines

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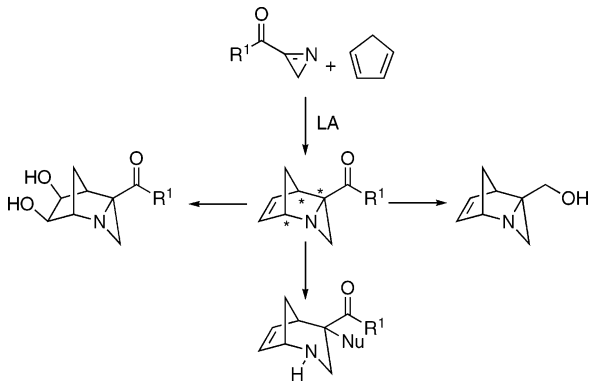
Asymmetric Diels−Alder reactions with 2*H*-azirines as dienophiles have been studied. Diastereoselective reactions with an enantiopure azirine **1b**, bearing a chiral auxiliary, gave substituted bi- and tricyclic tetrahydropyridines in high yield and stereoselectivity, under the influence of a Lewis acid. The novel enantioselective [4+2] cycloaddition reaction of 3-benzyl-2*H*-azirine carboxylate with cyclopentadiene was investigated with various chiral Lewis acid complexes and provided the corresponding tetrahydropyridines in moderate to low yield and enantioselectivity.

Introduction

Nitrogen-containing heterocycles are versatile structures which often occur in natural products and frequently show biological activity.[1] During the enormous efforts to develop stereoselective reactions, various alkaloids have also been found to efficiently act as both ligands and chiral auxiliaries.[2,3] Furthermore, many structures pose great synthetic challenges and the development of efficient and stereoselective methods for their preparation is therefore attracting the interest of many organic chemists.

A reaction that is efficient and often highly stereoselective is the Diels−Alder reaction, which in one step generates six-membered rings with up to four new stereogenic centers.[4,5] The Diels−Alder reaction is equally valuable for the construction of heterocycles and there are numerous examples of oxygen- and nitrogen-containing dienes and dienophiles which have been used in this reaction.[6] Imines, which are the most commonly used aza-dienophiles, generally require activation by an electron-withdrawing group and a Lewis acid to participate in [4+2] cycloaddition reactions.[7,8] Azirines, highly strained three-membered unsaturated nitrogen-containing heterocycles with a reactive C=N bond, are more reactive than the corresponding acyclic imines and are therefore useful aza-dienophiles. Some examples of Diels−Alder reactions between aryl- and alkyl-substituted azirines and electron-poor dienes have been reported.[9] Activated azirines bearing a conjugated electron-withdrawing substituent, for example, an ester, amide, or phosphonate group, react also with less reactive aliphatic 1,3-dienes under thermal conditions.[10,11] The products obtained in these reactions contain a highly functionalized fused [4.1.0] ring system that may undergo further transformations.[12] Oxidation of the formed double bond, ring opening of the aziridine ring, and reduction or hydrolysis of the ester functionality are examples of transformations which would lead to a great number of interesting compounds, for instance unnatural α- as well as *β*-amino acids (Scheme 1).

SCHEME 1



Diels−Alder reactions between azirines and several dienes are known to give products with complete regio

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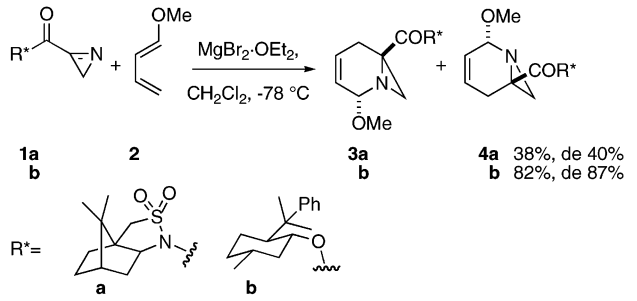
SCHEME 2



and endo selectivity (with respect to the three-membered ring).[10] However, until now only a few attempts to control the absolute stereochemistry in these reactions have been reported, all of which employ substrate control.[11,13] In one case the chiral information was part of the azirine ring itself, by an aromatic substituent in the 2-position, affording the corresponding cycloadduct in excellent selectivity.[11] Two attempts to govern the stereochemical outcome with chiral auxiliaries (Oppolzer's *N*,*N*-dialkyl-(1*R*)-isobornyl-10-sufonamide and (*S*)-phenylethylamide) attached to the 3-position of the azirine, i.e., a chiral azirine ester and amide, respectively, have been described, both resulting in low or no selectivity.[13]

Azirines show an inherent sensitivity toward acid-catalyzed decomposition. Despite this, previous work in our laboratory has shown it possible to enhance the reactivity of the azirines in Diels–Alder reactions by coordination to a Lewis acid.[14,15] It is well-known that Lewis acids often increase not only the rate of the Diels–Alder reactions but also the selectivities.[4] This proved to be true also for 2*H*-azirines substituted with a chiral auxiliary and the preliminary results were reported in a communication.[16] The most optimal approach to asymmetric synthesis and stereochemically pure compounds is, however, the use of chiral catalysts. This methodology has, as far as we know, not previously been applied to the cycloaddition reactions of azirines. Herein will be reported our results from the investigations of the asymmetric [4+2] cycloadditions of 2*H*-azirines with various dienes.

Results and Discussion

Auxiliary Controlled Diels–Alder Reactions. To study the substrate-controlled reaction, enantiomerically pure 2*H*-azirines **1a** and **1b** were chosen as substrates (Scheme 2). The dienophiles were reacted with 1-methoxy-1,3-butadiene (**2**) under thermal conditions as well as in the presence of a series of Lewis acids[17] to give **3a**,**4a** and **3b**,**4b**, respectively,[16,18] with complete regioselectivity and endo selectivity. It was clear from this study that

SCHEME 3

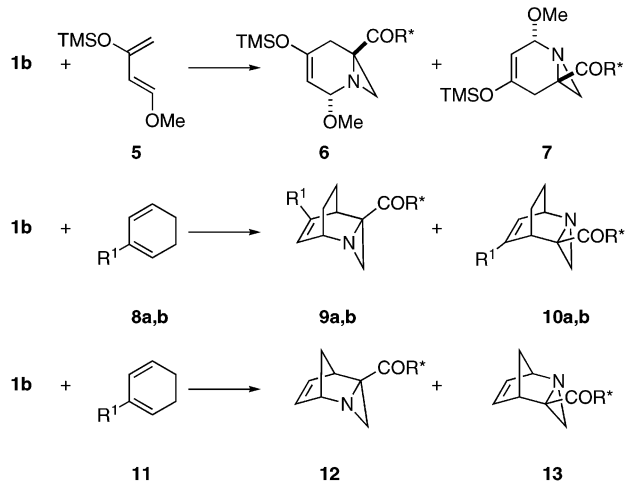


TABLE 1. Lewis Acid-Catalyzed Diels–Alder Reactions of Azirine 1b with Dienes 5, 8a, 8b, and 11

entry	diene	LA	*T* (°C)	products	de[a] (%)	yield (%)
1	**5**		−75 to −40	**6**, **7**	30	90
2	**5**	$MgBr_2{\cdot}OEt_2$	−100	**6**, **7**	96	56[b]
3	**5**	$ZnCl_2{\cdot}OEt_2$	−100 to −90	**6**, **7**	87	31[b]
4	**8a**		rt	**9a**, **10a**	20	100[c]
5	**8a**	$MgBr_2{\cdot}OEt_2$	−77	**9a**, **10a**		
6	**8a**	$ZnCl_2{\cdot}OEt_2$	−78	**9a**, **10a**	80	99
7	**8b**		−75 to −40	**9b**, **10b**	30	80[b]
8	**8b**	$MgBr_2{\cdot}OEt_2$	−75	**9b**, **10b**	97	99
9	**8b**	$ZnCl_2{\cdot}OEt_2$	−77	**9b**, **10b**	34	99
10	**11**		−78 to −40	**12**, **13**	8	99
11	**11**	$MgBr_2{\cdot}OEt_2$	−100	**12**, **13**	85	88[b,d]
12	**11**	$ZnCl_2{\cdot}OEt_2$	−100	**12**, **13**	58	99
13	**11**	$MgI_2{\cdot}(OEt_2)_x$	−78 to −40	*e*	78	100[d]
14	**11**	$MgBr_2$	−100 to −72	**12**, **13**	10	100[d]
15	**11**	$MgCl_2$	−78 to −40	**12**, **13**	15	100[d]
16	**11**	$YbCl_3$	−73	**12**, **13**	31	100[d]
17	**11**	$Mg(OTf)_2$	−100 to −72	**12**, **13**	17[f]	100
18	**11**	$ZnCl_2{\cdot}OEt_2$[g]	−77	**12**, **13**	19	54[b]
19	**11**	$BF_3{\cdot}OEt_2$	−77	**12**, **13**		

[a] Determined by ^{1}H NMR. [b] After chromatography. [c] Based on unreacted azirine. [d] Including ring-opened aziridine. [e] Only ring-opened aziridine was obtained. [f] Opposite major diastereomer compared to entries 10–16 and 18. [g] 10 mol %.

8-phenylmenthol was the auxiliary of choice, and with $MgBr_2{\cdot}OEt_2$ excellent de was obtained.

The obtained results encouraged us to determine the scope of this reaction with an additional set of dienes. Danishefsky's diene (**5**), cyclohexadiene (**8a**), 2-(trimethylsilyloxy)-1,3-cyclohexadiene (**8b**), and cyclopentadiene (**11**) were therefore selected and reacted with azirine **1b** (Scheme 3 and Table 1).

Cycloaddition of Danishefsky's diene with **1b** afforded **6** in 96% de in the presence of $MgBr_2{\cdot}OEt_2$ and in 87% de with $ZnCl_2{\cdot}OEt_2$ (entries 2 and 3). These results should be compared to 30% de obtained under thermal conditions (entry 1). It is clear that both Lewis acids greatly influence the stereochemical outcome in a positive way. In addition, the reaction time was significantly shortened to less than 10 min with $MgBr_2{\cdot}OEt_2$ compared to several days without Lewis acid. However, the yield of **6** and **7** after chromatography was unsatisfactory, which might be due to hydrolysis of the TMSO group. The reaction between azirine **1b** and cyclohexadiene in

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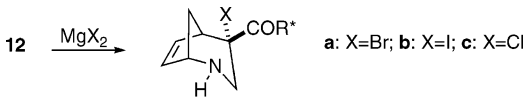
(18) The absolute configuration of **3a** and **4a** has not been determined.

SCHEME 4



14a,b,c

the presence of $MgBr_2 \cdot OEt_2$ gave no expected product despite complete consumption of the azirine (entry 5). For this diene $ZnCl_2 \cdot OEt_2$ proved to be a valuable complement and cycloadducts **9a**:**10a** were obtained as a 90:10 mixture in quantitative yield. This was a considerable increase in selectivity compared to the uncatalyzed reaction (compare entry 4 with entry 6). For the TMSO-substituted cyclohexadiene **8b** $MgBr_2 \cdot OEt_2$ was the Lewis acid of choice affording **9b** in 97% de in excellent yield, while no influence on the stereoselectivity was observed for $ZnCl_2 \cdot OEt_2$ (entries 8 and 9). Despite this, an increase in reaction rate was noticed for both Lewis acids. In the presence of $ZnCl_2 \cdot OEt_2$ or $MgBr_2 \cdot OEt_2$ the reaction of **1b** and cyclopentadiene was completed after less than 10 min at −100 °C. Also in this case $MgBr_2 \cdot OEt_2$ was superior to $ZnCl_2 \cdot OEt_2$ providing the product in good diastereoselectivity (entries 11 and 12). Another magnesium salt, $MgI_2 \cdot (OEt_2)_x$, also facilitated the cycloaddition reaction with a de of 78% (entry 13). However, to our surprise $MgBr_2$ and $MgCl_2$ did not exert any appreciable stereoselectivity (entries 14 and 15). A small selectivity was observed with $YbCl_3$ and $Mg(OTf)_2$ although the latter with opposite diastereomer **13** as major product (entries 16 and 17). Worth noting is that the formed cycloadducts can be separated by standard flash chromatography; this also makes reactions with less than excellent selectivities useful.

The strained aziridine moiety in **12** and **13** was found to easily undergo stereoselective ring opening by $YbCl_3$ and all the magnesium halides, of which $MgI_2 \cdot (OEt_2)_x$ was the most effective reagent for this transformation (Scheme 4).

Compound**14a**, obtained from major isomer **12**, was recrystallized and the absolute configuration determined by X-ray crystallography.[16] The other major cycloaddition products **3b**, **6**, **9a**, and **9b** were assigned in analogy. A few Lewis acids were then investigated to find a way to limit the undesired ring-opening reaction.[19] None of them showed the same ability to affect the stereoselectivity as did $MgBr_2 \cdot OEt_2$ and $MgI_2 \cdot (OEt_2)_x$. For the magnesium-based Lewis acids the etherate complexes are most efficient (compare entries 11 and 14). The reason for this still remains unclear, but might be due to different solubility. It is known that zinc halides, which are sparingly soluble in CH_2Cl_2, become more potent Lewis acids due to increased solubility when complexed to ether.[20] Despite the etherate complex, $MgBr_2 \cdot OEt_2$ is not completely soluble under the present reaction conditions.

The basicity of the formed cycloaddition products is believed to exceed that of the corresponding azirines,[21] leading to deactivation or inhibition of the Lewis acid. As a consequence, stoichiometric amounts of the Lewis acids are needed. However, we found that 10 mol % of $ZnCl_2 \cdot OEt_2$ was sufficient for complete conversion of **1b** in 4.5 h at −77 °C in the reaction with **11**, compared to days for the corresponding reaction in the absence of Lewis acid. This indicates catalytic behavior, albeit with low stereoselectivity (entry 18). A monodentate Lewis acid, $BF_3 \cdot OEt_2$, was applied but no product was obtained although all azirine was consumed (entry 19).

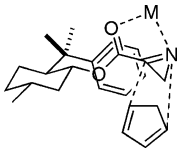


FIGURE 1.

The obtained configuration of the major 8-phenylmenthol-derived cycloadducts can be rationalized as follows.[22] It is assumed that the carbonyl group is aligned with the axial C(1) hydrogen in the cyclohexane ring and the phenyl group oriented parallel to the azirine nuclei. If the azirine ring is locked in an *s-cis* conformation by a chelating Lewis acid, the *Re*-face becomes shielded by the phenyl group and the cycloaddition therefore takes place on the *Si*-face of the azirine (Figure 1).

Enantioselective Diels−Alder Reactions. The development of catalytic enantioselective aza-Diels−Alder reactions with imines as dienophiles has only recently been addressed,[7,23] and to the best of our knowledge, the use of azirines as dienophiles in these reactions has not yet been reported. There are a few obstacles with imines as dienophiles in catalytic enantioselective Diels−Alder reactions that have to be considered to achieve useful reactions: the Lewis basic nitrogens in both imines and product (vide supra), the flexible *E*/*Z* conformations which generate several possible reactive conformers, the low reactivity, and unstable substrates. However, azirines have the potential to overcome some of the mentioned drawbacks, such as fewer conformations, due to a cyclic imine moiety with the lone pair electrons in a well-defined position, and a higher reactivity. On the other hand, the acid sensitivity of the azirines as well as of the products requires fine-tuned Lewis acid−ligand complexes which have to be potent enough to promote the cycloadditions but not destroy the azirine and the aziridine.

In this study a wide range of Lewis acidic metals and ligands, which have previously shown excellent results in Diels−Alder reactions, have been screened together with benzyl-2*H*-azirine-3-carboxylate **15** as dienophile and cyclopentadiene (**11**) (Scheme 5 and Figure 2).[3,22−25] Some representative results are collected in Table 2.

The uncatalyzed reaction proceeded smoothly, and clean conversion of azirine **15** into **16** was obtained in less than 15 min at room temperature. Product formation was evident after 15 min also at lower temperatures (−40 and −78 °C), and the cycloadducts predominated after

(19) In addition to $Mg(OTf)_2$ (presented in Table 1), also $Yb(OTf)_3$, $Ti(OiPr)_4$, and $SnCl_4$ were screened.

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(24) Azirine **15** was prepared by thermolysis from the corresponding vinyl azide.[27] The vinyl azide was obtained in two steps, using a slightly modified literature procedure, starting from benzyl acrylate. Gilchrist, T. L.; Mendonca, R. *Synlett* **2000**, 1843−1845.

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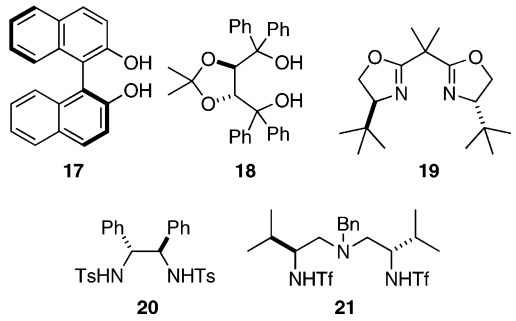


FIGURE 2. Ligands used in the Diels–Alder reactions of azirine **15**.

SCHEME 5

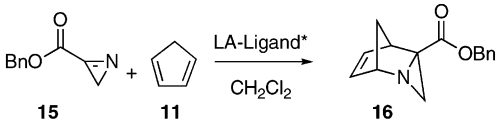


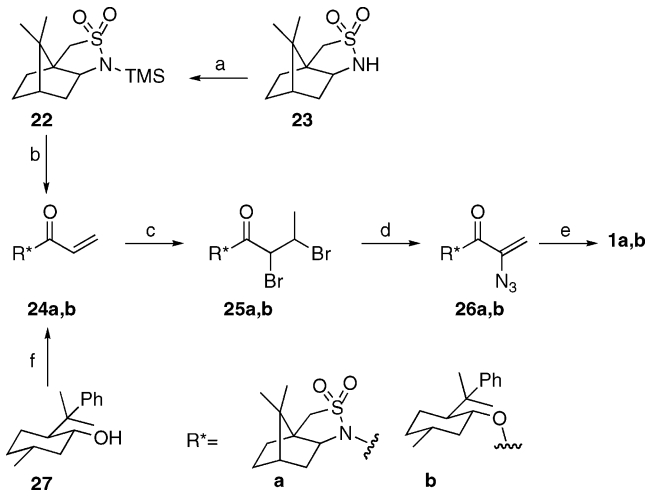
TABLE 2. Enantioselective Diels–Alder Reactions of Azirine 15 with Cyclopentadiene

entry	LA	ligand	*T* (°C)	ee[a] (%)	yield[b] (%)
1			−40		75
2	$AlMe_3$	**17**	−35	51	41
3	$AlMe_3$	**18**	−40	35	27
4	$Mg(ClO_4)_2$	**19**	−40		
5	$Mg(ClO_4)_2$[c]	**19**	−40	32	22
6	$Mg(ClO_4)_2$[c]	**19**	−60	52	25
7	$AlMe_3$	**20**	−60	12	22
8	$AlMe_3$	**21**	−60	19	20

[a] Determined by chiral HPLC, Chiralcel, OD-H. [b] After chromatography. [c] In the presence of 4 Å molecular sieves.

1.5 h at −40 °C (entry 1). The reactions were, therefore, conducted with a stoichiometric amount of catalyst to limit the background reaction. Of all the Lewis acids screened, $AlMe_3$ together with especially oxygen-containing but also nitrogen-containing ligands proved to be most successful (entries 2, 3, 7, and 8). (*S*)-BINOL (**17**) gave together with $AlMe_3$ **16** in 50% enantiomeric excess (ee) and 41% yield (entry 2). Both the selectivity and yield dropped slightly when using TADDOL (**18**) as ligand (entry 3). With bissulfonamide ligands **20** and **21** low selectivities and yields were obtained (entries 7 and 8). Aluminum-based Lewis acids are among those considered to be strongly acidic, particularly compared to magnesium and zinc Lewis acids, which showed excellent results in the auxiliary controlled Diels–Alder reactions. Despite the acidity of $AlMe_3$, its complexes did not affect the reactivity of the cycloaddition in a positive way. In an attempt to increase the reaction rate, $AlMe_3$ was exchanged for $AlMe_2Cl$ in the reactions using ligands **17** and **18**, but no product was obtained in either case. Ligand **19** was then investigated together with $Cu(OTf)_2$, $Zn(OTf)_2$, $Mg(ClO_4)_2$, $MgI_2{\cdot}(OEt_2)_x$, and $FeCl_3$. Depending on the Lewis acid employed the azirine remained unchanged or was rapidly consumed without any appreciable formation of **16**. However, cycloadduct **16** was obtained in 32% ee and 22% yield when a combination of powdered 4 Å molecular sieves and a catalyst formed from ligand **19** and $Mg(ClO_4)_2$ was applied (entry 5). At a lower reaction temperature, −60 °C, the ee increased to 52%, while the yield was essentially the same (entry 6). Both the reaction conducted at −40 °C and the one at −60 °C were considerably faster than the aluminum-catalyzed reactions, with no azirine remaining after 40 min and 4 h, respectively. For some combinations of Lewis acids and ligands the reactions were slow and azirine was still present after prolonged reaction times. Yet, for other combinations the azirine was consumed directly, leaving no desired product after workup. The low to moderate yields obtained after purification in all reactions employing chiral catalysts indicated degradation of either the azirine and/or the product. This may, thus, be caused by decomposition during chromatography,[26] by the Lewis acids, or simply by decomposition of the unstable azirine over time.

SCHEME 6[a]



[a] Reagents and conditions: (a) TMSCl, Et_3N, CH_3CN, PhMe.[28] (b) acryloyl chloride, $CuCl_2$, PhMe.[28] (c) Br_2, CH_2Cl_2; **a**: rt, 81%; **b**: 50 °C, 95%. (d) NaN_3, DMF; **a**: 60 °C, 56%; **b**: 85 °C, 65%. (e) CH_2Cl_2, 150 °C, 20 min; **a** and **b**: >95%. (f) Acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C.[29]

Synthesis of Chiral Azirines 1a and 1b. The auxiliary derivatized azirines **1a** and **1b** were synthesized in good yields via the corresponding acrylates, which were converted into the dibromides and then further into the vinyl azides (Scheme 6). The vinyl azides were then cleanly transformed into the corresponding azirines by thermolysis at 150 °C in CH_2Cl_2 for 20 min.[27] No purification was necessary and the azirines were immediately used in the cycloaddition reactions.

Conclusions

Herein is described a novel Lewis acid-catalyzed asymmetric [4+2] cycloaddition reaction of 2*H*-azirines with various dienes affording adducts comprising a fused tetrahydropyridine–aziridine moiety. The enantioselective Diels–Alder reaction of benzyl-2*H*-azirine-3-carboxylate has, under the investigated reaction conditions, not

(26) Loss of product was observed on both silica and aluminum oxide.
(27) Sjöholm Timén, Å.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339–5341.
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given useful levels of enantioselectivity and yield. On the other hand, the auxiliary controlled Diels−Alder reactions of azirine **1b** proved to produce the cycloaddition products in a highly efficient way. The high levels of stereoselectivity and yields obtained in the reactions with a variety of dienes, the easy separations of the formed diastereomers, and the convenient preparation of the chiral azirines as well as removal of the auxiliary from the adducts[12] make this a valuable method for the asymmetric synthesis of fused nitrogen-containing heterocycles. We find, at this stage, the auxiliary based approach superior to the enantioselective approach.

Experimental Section

This Experimental Section contains general procedures for the Lewis acid mediated Diels−Alder reactions of azirines **1a**, **1b**, and **15** and analytical data of all cycloadducts. A general procedure for the ring-opening reaction of aziridines **12a**, **12b**, and **12c** and analytical data of the corresponding products **14a**, **14b**, and **14c** are also reported. For general experimental details and procedures for preparation of **25a**, **25b**, **26a**, **26b**, **1a**, and **1b** and their analytical data, seethe Supporting Information.

General Procedure for Lewis Acid-Mediated Diels−Alder Reaction of 2*H*-Azirines 1a and 1b Forming Cycloadducts 3b and 4b. Freshly prepared azirine **1b** (20 mg, 67 μmol) and $ZnCl_2$·OEt_2 (47 μL, 134 μmol) were stirred in dry CH_2Cl_2 (1.3 mL) at −100 °C for 20 min before addition of 1-methoxybutadiene (13 μL, 134 μmol). Complete consumption of **1b** was indicated by TLC after 10 min and $NaHCO_3$ (aq, 1 mL) was added. The two-phase mixture was then vigorously stirred at room temperature for 20 min before filtration through an Extrelute tube, which was rinsed with CH_2Cl_2 (15 mL). The resulting organic phase was evaporated and the diastereoselectivity determined by ^{1}H NMR. The crude product was purified by flash chromatography (SiO_2, pentane−EtOAc) to afford cycloadducts **3b** (14 mg,37 μmol, 56%) and **4b** (2 mg, 4 μmol, 6%) as oils. Analytical data for **3b**: $[\alpha]^{25}_D$ +61 (*c* 0.43, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.31 (m, 4H), 7.12 (br t, J = 6.8 Hz, 1H), 5.57 (m, 1H), 5.36 (m, 1H), 4.83 (td, J = 10.8, 4.5 Hz, 1H), 4.72 (br s, 1H), 3.60 (s, 3H), 2.27 (br dd, J = 18.6, 2.3 Hz, 1H), 2.02 (ddd, J = 12.3, 20.8, 3.5 Hz, 1H), 1.91 (s, 1H), 1.90 (s, 1H), 1.87−1.95 (m, 2H), 1.64 (m, 2H), 1.42−1.52 (m, 1H), 1.33 (s, 3H), 1.24 (s, 3H), 1.03−1.14 (m, 1H), 0.96 (app q, J = 11.1 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H), 0.80−0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.4, 128.0, 125.5, 125.0, 124.0, 123.4, 85.7, 75.5, 56.4, 50.5, 41.7, 39.8, 37.9, 34.5, 31.2, 29.1, 27.5, 26.8, 26.1, 21.8, 21.5; HRMS (FAB+) calculated for $C_{24}H_{34}NO_3$ (M + H) 384.2539, foun: 384.2537.

Analytical data for **4b**: $[\alpha]^{25}_D$ −87 (*c* 0.47, CH_2Cl_2); IR (neat) ν_{max} 2955, 2922, 1716, 1256, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.31 (m, 4H), 7.07 (br tt, J = 7.1, 1.3 Hz, 1H), 5.55 (m, 1H), 5.34 (m, 1H), 4.95 (td, J = 10.8, 4.5 Hz, 1H), 4.69 (br s, 1H), 3.60 (s, 3H), 2.17 (br dd, J = 18.7, 6.1 Hz, 1H), 2.08 (ddd, J = 12.3, 10.8, 3.8 Hz, 1H), 1.77 (s, 1H), 1.75−1.84 (m, 3H), 1.71 (s, 1H), 1.66 (m, 1H), 1.42−1.52 (m, 1H), 1.33 (s, 3H), 1.20 (s, 3H), 1.08−1.18 (m, 1H), 0.98 (app q, J = 12.1 Hz, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.84−0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.9, 127.9, 125.4, 125.0, 124.2, 123.0, 85.7, 75.1, 56.5, 50.3, 41.7, 39.6, 37.9, 34.5, 31.3, 28.8, 28.4, 26.5, 24.1, 21.8, 21.2; HRMS (FAB+) calcd for $C_{24}H_{34}NO_3$ (M + H) 384.2539, found 384.2542.

Cycloadducts 3a and 4a. 3a and **4a** were prepared from azirine **1a** and diene **2** as described for **3b** and **4b** and obtained as a colorless semisolid. Analytical data for the **major isomer**: $[\alpha]^{25}_D$ +139 (*c* 0.32, CH_2Cl_2); IR (neat) ν_{max} 1687, 1328, 1134, 1109; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (m, 1H), 5.48 (m, 1H), 4.89 (br s, 1H), 3.89 (dd, J = 7.6, 5.0 Hz, 1H), 3.60 (s, 3H), 3.43 (s, 2H), 2.70 (A-part of split ABq, J = 17.9, 6.0 Hz, 1H), 2.55 (B-part of split ABq, J = 17.4, 2.0 Hz, 1H), 2.18 (s, 1H), 2.09 (s, 1H), 2.04−2.16 (m, 2H), 1.89 (m, 3H), 1.33−1.47 (m, 2H), 1.13 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 124.3, 123.0, 84.7, 65.4, 56.5, 53.1, 48.8, 47.9, 44.2, 42.3, 38.1, 32.7, 27.3, 26.5, 22.9, 20.6, 19.9; HRMS (FAB+) calcd for $C_{18}H_{27}N_2O_4S$ (M + H) 367.1692, found 367.1707.

Analytical data for the **minor isomer**: $[\alpha]^{25}_D$ −7 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (m, 1H), 5.46 (m, 1H), 4.90 (br s, 1H), 3.98 (dd, J = 7.7, 4.8 Hz, 1H), 3.63 (s, 3H), 3.48 (A-part of ABq, J = 13.6 Hz, 1H), 3.38 (B-part of ABq, J = 13.6 Hz, 1H), 2.93 (dd, J = 18.0, 6.2 Hz, 1H), 2.35 (br dd, J = 18.3, 2.2 Hz, 1H), 2.19 (s, 1H), 2.05 (m, 1H), 2.01 (s, 1H), 1.86−1.98 (m, 4H), 1.32−1.42 (m, 2H), 1.18 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 124.3, 123.0, 84.8, 66.2, 56.6, 53.9, 48.2, 47.6, 45.1, 41.7, 38.6, 33.4, 28.2, 26.3, 23.0, 21.4, 19.9; HRMS (FAB+) calcd for $C_{18}H_{27}N_2O_4S$ (M + H) 367.1692, found 367.1688.

Cycloadducts 6 and 7. 6 and **7** were prepared from azirine **1b** and diene **5** as described for **3b** and **4b** and obtained as a colorless oil. Analytical data for **6**: $[\alpha]^{25}_D$ +44 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.31 (m, 4H), 7.12 (m, 1H), 4.88 (br s, 1H), 4.83 (td, J = 10.8, 4.5 Hz, 1H), 4.46 (m, 1H), 3.59 (s, 3H), 2.37 (br d, J = 18.1 Hz, 1H), 2.01 (m, 1H), 1.88−1.94 (m, 4H), 1.60−1.68 (m, 2H), 1.41−1.52 (m, 1H), 1.34 (s, 3H), 1.24 (s, 3H), 1.08 (app qd, J = 12.6, 3.8 Hz, 1H), 0.97 (q, J = 12.0 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H), 0.79−0.89 (m, 1H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.2, 148.1, 128.0, 125.5, 125.2, 99.2, 87.9, 75.6, 56.4, 50.4, 41.7, 39.9, 38.9, 34.6, 31.3, 29.4, 27.3, 26.8, 26.7, 26.4, 21.8, 0.1; HRMS (FAB+) calcd for $C_{27}H_{42}NO_4Si$ (M + H) 472.2883, found 472.2877.

Analytical data for **7**: $[\alpha]^{25}_D$ −85 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.30 (m, 4H), 7.07 (br t, J = 7.2 Hz, 1H), 4.96 (td, J = 10.7, 4.3 Hz, 1H), 4.85 (br s, 1H), 4.43 (m, 1H), 3.59 (s, 3H), 2.06−2.11 (m, 2H), 1.91 (br d, J = 18 Hz, 1H), 1.79 (m, 2H), 1.74 (s, 1H), 1.67 (s, 1H), 1.66 (m, 1H), 1.41−1.51 (m, 1H), 1.33 (s, 3H), 1.20 (s, 3H), 1.14 (app qd, J = 12.8, 3.6 Hz, 1H), 0.98 (app q, J = 12.2 Hz, 1H), 0.87 (d, J = 6.7 Hz, 3H), 0.85−0.93 (m, 1H), 0.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 151.8, 148.2, 127.9, 125.4, 125.0, 98.9, 88.0, 75.1, 56.5, 50.3, 41.7, 39.6, 38.7, 34.5, 31.3, 28.9, 28.7, 26.5, 26.4, 24.0, 21.8, 0.2; HRMS (FAB+) calcd for $C_{27}H_{42}NO_4Si$ (M + H) 472.2883, found 472.2898.

Cycloadducts 9a and 10a. 9a and **10a** were prepared from azirine **1b** and diene **8a** as described for **3b** and **4b** and obtained as a colorless oil. Analytical data for **9a**: $[\alpha]^{25}_D$ +40 (*c* 0.23, CH_2Cl_2); IR (neat) ν_{max} 2952, 2921, 1727, 1229; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 4H), 7.13 (m, 1H), 5.97 (m, 1H), 5.56 (m, 1H), 4.90 (td, J = 10.6, 4.3 Hz, 1H), 3.79 (m, 1H), 2.31 (m, 1H), 2.07 (ddd, J = 12.2, 10.6, 3.5 Hz, 1H), 1.81−1.90 (m, 2H), 1.62−1.74 (m, 2H), 1.51 (s, 1H), 1.40−1.51 (m, 1H), 1.30 (s, 3H), 1.24 (s, 1H), 1.22 (s, 3H), 1.19−1.27 (m, 1H), 1.09 (app qd, J = 12.6, 3.5 Hz, 1H), 0.97 (app q, J = 12.1 Hz, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.82−1.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 151.9, 130.9, 127.9, 125.4, 125.2, 124.9, 74.9, 52.3, 50.5, 41.7, 39.7, 39.3, 34.6, 31.2, 29.1, 28.6, 28.0, 26.6, 24.9, 24.1, 21.8, 20.4; HRMS (FAB+) calcd for $C_{25}H_{34}NO_2$ (M + H) 380.2590, found 380.2591.

Analytical data for **10a**: $[\alpha]^{25}_D$ −63 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.13 (m, 1H), 6.14 (m, 1H), 5.57 (m, 1H), 4.98 (td, J = 10.6, 4.5 Hz, 1H), 3.80 (m, 1H), 3.12 (m, 1H), 2.06 (ddd, J = 12.3, 10.6, 3.5 Hz, 1H), 1.73−1.89 (m, 3H), 1.30 (s, 3H), 1.25−1.59 (m, 4H), 1.20 (s, 3H), 1.09 (s, 1H), 1.01 (s, 1H), 0.97−1.13 (m, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.78−0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 151.2, 131.0, 128.0, 125.5, 125.23, 125.17, 75.2, 52.5, 49.7, 41.6, 40.0, 38.6, 34.4, 31.3, 29.6, 27.0, 26.9, 26.5, 24.1, 21.7, 20.5; HRMS (FAB+) calcd for $C_{25}H_{34}NO_2$ (M + H) 380.2590, found 380.2587.

Cycloadducts 9b and 10b. 9b and **10b** were prepared from azirine **1b** and diene **8b** as described for **3b** and **4b** and obtained as a colorless oil. Analytical data for **9b**: $[\alpha]^{25}_D$ +68 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.29 (m,

4H), 7.12 (m, 1H), 4.95 (td, J = 10.6, 4.5 Hz, 1H), 4.49 (dd, J = 6.3, 2.5 Hz, 1H), 3.81 (m, 1H), 2.66 (q, J = 2.6 Hz, 1H), 2.00 (ddd, J = 12.2, 10.6, 3.5 Hz, 1H), 1.77−1.87 (m, 2H), 1.54 (s, 1H), 1.50−1.62 (m, 3H), 1.42 (s, 1H), 1.41−1.49 (m, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.20−1.31 (m, 2H), 0.98 (app q, J = 12.1 Hz, 1H), 0.97−1.07 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H), 0.75−0.87 (m, 1H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 154.1, 151.0, 127.9, 125.5, 125.4, 96.8, 75.0, 52.8, 50.5, 41.8, 40.0, 39.4, 35.4, 34.5, 31.3, 28.7, 27.1, 26.8, 26.2, 25.5, 21.8, 21.1, 0.1; HRMS (FAB+) calcd for $C_{28}H_{42}NO_3Si$ (M + H) 468.2934, found 468.2933.

Analytical data for **10b**: $[\alpha]^{25}_D$ −96 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.13 (m, 1H), 4.97 (td, J = 10.7, 4.3 Hz, 1H), 4.49 (dd, J = 6.4, 2.7 Hz, 1H), 3.79 (m, 1H), 3.02 (br d, J = 2.1 Hz, 1H), 2.05 (ddd, J = 12.2, 10.6, 3.4 Hz, 1H), 1.78 (m, 3H), 1.49−1.57 (m, 2H), 1.38−1.47 (m, 1H), 1.30 (s, 3H), 1.25−1.35 (m, 2H), 1.24 (s, 1H), 1.20 (s, 3H), 1.08 (app q, J = 12.2 Hz, 1H), 1.00 (s, 1H), 0.97−1.11 (m, 1H), 0.85 (d, J = 6.4 Hz, 3H), 0.75−0.88 (m, 1H), 0.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 154.3, 151.2, 128.0, 125.5, 125.2, 96.9, 75.2, 53.1, 49.6, 41.6, 40.0, 38.8, 35.9, 34.4, 31.3, 29.7, 27.1, 26.9, 26.4, 25.4, 21.7, 21.0, 0.1; HRMS (FAB+) calcd for $C_{28}H_{42}NO_3Si$ (M + H) 468.2934, found 468.2953.

Cycloadducts 12 and 13. 12 and **13** were prepared from azirine **1b** and diene **11** as described for **3b** and **4b** and obtained as a colorless oil. Analytical data for **12**: $[\alpha]^{25}_D$ +51 (*c* 0.42, CH_2Cl_2); IR (neat) ν_{max} 2953, 2918, 1724, 1238; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.30 (m, 4H), 7.13 (br t, J = 6.8 Hz, 1H), 5.95 (m, 1H), 5.54 (br dd, J = 5.3, 2.3 Hz, 1H), 4.93 (td, J = 10.8, 4.5 Hz, 1H), 3.99 (br s, 1H), 2.52 (m, 1H), 2.36 (d, J = 2.8 Hz, 1H), 2.06 (ddd, J = 12.3, 3.8 Hz, 1H), 1.88 (m, 2H), 1.76 (app dq, J = 13.4, 3.4 Hz, 1H), 1.59−1.69 (m, 2H), 1.51 (s, 1H), 1.43−1.52 (m, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 1.12 (app qd, J = 12.8, 3.3 Hz, 1H), 0.96 (app q, J = 12.0 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H), 0.83−0.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 151.8, 133.3, 127.9, 127.6, 125.4, 125.0, 75.0, 66.1, 60.5, 50.5, 43.5, 43.4, 43.2, 41.6, 39.6, 34.5, 31.2, 28.4, 26.5, 24.5, 21.8; HRMS (FAB+) calcd for $C_{24}H_{32}NO_2$ (M + H) 366.2433, found 366.2426.

Analytical data for **13**: $[\alpha]^{25}_D$ −98 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.26 (m, 4H), 7.10 (br tt, J = 6.4, 2.1 Hz, 1H), 6.11 (m, 1H), 5.58 (dd, J = 5.0, 2.3 Hz, 1H), 4.96 (td, J = 10.6, 4.3 Hz, 1H), 3.99 (br s, 1H), 3.33 (m, 1H), 2.04 (m, 2H), 1.87 (m, 1H), 1.71 (m, 2H), 1.56−1.66 (m, 2H), 1.39−1.51 (m, 1H), 1.31 (s, 3H), 1.26 (s, 1H), 1.20 (s, 3H), 1.00−1.13 (m, 2H), 0.86 (d, J = 6.5 Hz, 3H), 0.79−0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 151.4, 133.2, 127.9, 125.4, 125.0, 75.2, 66.1, 60.7, 50.1, 44.4, 43.0, 42.0, 41.6, 39.8, 34.5, 31.3, 27.5, 26.7, 25.7, 21.7; HRMS (FAB+) calcd for $C_{24}H_{32}NO_2$ (M + H) 366.2433, found 366.2428.

General Procedure for the Synthesis of (−)-8-Phenylmenthol-Derived Aza-bicyclo[3.2.1]octenes 14a, 14b, and 14c. Aziridine **12** (10 mg, 27 μmol) was added to a suspension of MgI_2·OEt_2 (22 mg, 60 μmol) in CH_2Cl_2 (1 mL) at −65 °C. TLC indicated complete consumption of the aziridine after 2 h and $NaHCO_3$ (aq, 0.5 mL) was added. The two-phase mixture was stirred before filtration through an Extrelute tube, which was rinsed with CH_2Cl_2 (15 mL). The resulting organic phase was concentrated before purification by preparative HPLC (Zorbax Rx-SIL, hexane:*i*-PrOH, 99:1), which gave **14b** as a colorless oil (8 mg, 45%). Analytical data: $[\alpha]^{25}_D$ −91 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.18 (m, 1H), 6.35 (dd, J = 5.8, 2.8 Hz, 1H), 6.15 (dd, J = 5.8, 2.8 Hz, 1H), 4.94 (td, J = 10.6, 4.3 Hz, 1H), 3.79 (br t, J = 3.0 Hz, 1H), 3.60 (s, 2H), 3.31 (dd, J = 5.5, 2.8 Hz, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.97 (ddd, J = 11.6, 5.5, 3.5 Hz, 1H), 1.53−1.68 (m, 3H), 1.49 (s, 3H), 1.42 (s, 1H), 1.37−1.42 (m, 1H), 1.30 (s, 3H), 0.93−1.08 (m, 2H), 0.89 (d, J = 6.3 Hz, 3H), 0.76−0.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 150.7, 137.1, 132.8, 128.1, 125.7, 125.5, 78.0, 55.7, 51.6, 50.1, 49.4, 46.1, 40.6, 40.3, 34.5, 31.3, 29.5, 27.4, 26.9, 25.0, 21.8; HRMS (FAB+) calcd for $C_{24}H_{33}INO_2$ (M + H) 494.1556, found 494.1551.

(−)-8-Phenylmenthol-Derived Aza-bicyclo[3.2.1]octene 14a. 14a was obtained as colorless crystals. Analytical data: mp 120−121 °C; $[\alpha]^{25}_D$ −50 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.18 (m, 1H), 6.36 (dd, J = 5.5, 2.5 Hz, 1H), 6.13 (dd, J = 5.5, 2.8 Hz, 1H), 4.91 (td, J = 10.8, 4.3 Hz, 1H), 3.77 (br t, J = 3.0 Hz, 1H), 3.60 (d, J = 13.8 Hz, 1H), 3.36 (d, J = 13.8 Hz, 1H), 3.24 (dd, J = 5.3, 2.5 Hz, 1H), 2.11 (m, 1H), 2.04 (m, 2H), 1.46 (s, 3H), 1.45−1.58 (m, 4H), 1.38 (m, 1H), 1.30 (s, 3H), 0.93−1.07 (m, 2H), 0.88 (d, J = 6.3 Hz, 3H), 0.80 (app qd, J = 12.3, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 150.5, 135.9, 132.9, 128.1, 125.8, 125.4, 78.0, 61.7, 55.7, 50.3, 49.6, 48.1, 45.8, 40.9, 40.3, 34.4, 31.3, 29.8, 27.4, 24.5, 21.8; HRMS (FAB+) calcd for $C_{24}H_{33}BrNO_2$ (M + H) 446.1695, found 446.1703.

(−)-8-Phenylmenthol-Derived Aza-bicyclo[3.2.1]octene 14c. 14c was obtained as a colorless oil (3 mg, 55%). $[\alpha]^{25}_D$ −42 (*c* 0.18, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.17 (tt, J = 6.6, 1.9 Hz, 1H), 6.37 (dd, J = 5.8, 2.7 Hz, 1H), 6.13 (dd, J = 5.8, 2.7 Hz, 1H), 4.89 (td, J = 10.4, 4.1 Hz, 1H), 3.79 (m, 1H), 3.59 (d, J = 13.7 Hz, 1H), 3.18 (d, J = 13.7 Hz, 1H), 3.13 (dd, J = 5.3, 2.7 Hz, 1H), 1.97−2.10 (m, 3H), 1.55 (m, 1H), 1.44 (s, 3H), 1.43−1.50 (m, 2H), 1.39 (m, 1H), 1.30 (s, 3H), 1.26 (br s, 1H), 0.94−1.05 (m, 2H), 0.88 (d, J = 6.3 Hz, 3H), 0.79 (app qd, J = 12.5, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 150.4, 135.7, 132.9, 128.1, 125.8, 125.4, 77.9, 66.8, 55.9, 50.4, 49.2, 47.8, 44.4, 41.0, 40.3, 34.5, 31.3, 29.9, 27.4, 24.5, 21.8; HRMS (FAB+) calcd for $C_{24}H_{33}ClNO_2$ (M + H) 402.2200, found 402.2191.

General Procedure for the Chiral Lewis Acid-Mediated Diels–Alder Reaction of 2*H*-Azirine 15 Forming Cycloadducts 16.[14] A solution of $AlMe_3$ in Hexanes (2 M, 114 μL, 0.23 mmol) was added dropwise to a solution of (*S*)-BINOL (65 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) at room temperature. The Lewis acid–ligand mixture was stirred at room temperature for 30 min before being cooled to −35 °C. A solution of **15** (35 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added before addition of diene **11** (17 μL, 0.21 mmol). $NaHCO_3$ (aq, 1 mL) was added after 24 h and the two-phase mixture was then vigorously stirred at room temperature for 20 min before filtration through an Extrelute tube, which was rinsed with CH_2Cl_2 (15 mL). The organic phase was concentration in vacuo and purified by flash chromatography (SiO_2, pentane−EtOAc) to afford cycloadducts **16** as an oil in 41% yield. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, hexane:*i*-PrOH, 90:10, 0.6 mL/min).

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Supporting Information Available: Procedures for the synthesis of dibromides **25a** and **25b**, vinyl azides **26a** and **26b**, and azirines **1a** and **1b**, and their analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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