JOC Article

Asymmetric Hetero-Diels−Alder Reactions of *N*-Sulfinyl Dienophiles Using Chiral Bis(oxazoline)−Copper(II) and −Zinc(II) Triflates

Annette Bayer,[†] Molla Mellese Endeshaw,[‡] and Odd R. Gautun*[,‡]

Department of Chemistry, University of Tromsø, NO-9037 Tromsø, Norway, and Department of Chemistry, Norwegian University of Science and Technology (NTNU), NO-7491 Trondheim, Norway

odd.gautun@chem.ntnu.no

Received June 10, 2004

Asymmetric hetero-Diels−Alder (HDA) reactions of *N*-sulfinyl dienophiles using bis(oxazoline)−copper(II) and −zinc(II) triflates are described. The cycloadditions with cyclic and acyclic 1,3-dienes have been studied. In most cases, good enantioselectivities (70−98% ee) and yields (60−85%) were obtained with stoichiometric amounts of the Lewis acids. Cyclic dienes gave the endo adducts as major products, while acyclic dienes provided cis adducts. The HDA adducts have been transformed into N-protected α-amino acid methyl esters, amino alcohols, and homoallylic amines. A stereochemical model, which accounts for the enantiofacial selectivity of the HDA reaction by a tetrahedral metal center, has been proposed. Mechanistic studies revealed positive nonlinear effects, assumed to arise from the formation of less-reactive heterochiral complexes. Investigation of the temperature dependence of the enantioselectivity indicated that at least two selective reaction steps exist in the zinc-catalyzed reaction. Reactions run with 10 mol % chiral Lewis acid gave poor yields and selectivities. However, in combination with TMSOTf (100 mol %), high yields (68−86%) and enantioselectivities (97−98% ee) were obtained.

Introduction

Stereoselective catalysis is an important research field in chemistry. Our interests lie in the development of reactions for the stereoselective introduction of nitrogen into organic compounds. We recently described preliminary findings on bis(oxazoline)−copper(II)- and −zinc(II)-catalyzed heterocyclic Diels−Alder (HDA) reactions of *N*-sulfinyl compounds.[1] Here, we present more comprehensive studies of the scope and limitations of this reaction and mechanistic aspects concerning the stereoselectivity, such as nonlinear effects and temperature dependence. The resulting heterocycles have been transformed into useful intermediates, such as α-amino acids, vicinal amino alcohols, and homoallylic amines.[2]

Results and Discussion

Stoichiometric Reactions. Initially, a series of chiral Lewis acids were investigated as catalysts for the stereoselective HDA reaction of *N*-sulfinyl dienophiles **1a**[3] and **1b**[4] with 1,3-cyclohexadiene (Scheme 1). The Lewis acids were generated in situ from bis(oxazolines) **3** and **4**,[5] bisiminocyclohexane **5**,[6] and BINAP **6** ligands (Figure 1) in combination with metal salts such as $CuClO_4$·4MeCN, CuOTf·$^1/_2C_6H_6$, $Cu(OTf)_2$, $CuBr_2$·2$AgSbF_6$, $Mg(OTf)_2$, $Sn(OTf)_2$, $Zn(OTf)_2$, $ZnBr_2$, $ZnBr_2$·2$AgSbF_6$, $Pd(PhCN)_2Cl_2$·2$AgBF_4$,[7] $In(OTf)_3$, and $Sc(OTf)_3$.

Some representative and more promising results are shown in Table 1. We found that stoichiometric amounts of **3a**−$Cu(OTf)_2$ and −$Zn(OTf)_2$ were best suited to promote the HDA reaction of **1a** and **1b** with 1,3-cyclohexadiene. These reactions (entries 2, 9, 12, and 13 in Table 1) provided the endo adducts **2a** (X = Cbz)[8,9] and **2b** (X = Ts)[8,9] in good enantioselectivities (90−98% ee), diastereoselectivities (>90% de), and yields (63−85%). For comparison, HDA reactions mediated by the Lewis acid prepared from diol **7**[10] and Me_2TiCl_2 [11] gave

* To whom correspondence should be addressed.
[†] University of Tromsø.
[‡] NTNU.

(1) Bayer, A.; Gautun, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2937−2939.

(2) For transformations into other intermediates, see: Weinreb, S. M. *Acc. Chem. Res.* **1988**, *21*, 313−318.

(3) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861−7867. According to the reference, *trans*-**12a** is a solid and *cis*-**12a** an oil. However, in comparison with the spectral data, we observed that the compound reported as *trans*-**12a** was an oil and *cis*-**12a** a solid.

(4) Kresze, G.; Wucherpfenning, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 149−167.

(5) For the preparation of the bis(oxazolinyl)pyridines, see: (a) Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629−9630. For the preparation of the bis(oxazolines), **3a**, see: (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728−729. For **3b**, see: (c) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4551−4544. For reduction of the amino acids, see: (d) McKennon, M. J.; Meyers, A. I.; Dauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568−3571.

(6) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027−7030.

(7) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253−6256.

(8) Bayer, A.; Gautun, O. R. *Tetrahedron Lett.* **2000**, *41*, 3743−3746.

(9) Bayer, A.; Hansen, L. K.; Gautun, O. R. *Tetrahedron: Asymmetry* **2002**, *13*, 2407−2415.

10.1021/jo0490245 CCC: $27.50
Published on Web 09/11/2004

TABLE 1. HDA Reactions of 1a or 1b with 1,3-Cyclohexadiene Promoted by Chiral Copper- and Zinc-Based Lewis Acids

entry	dienophile	ligand	metal (100 mol %)	*T*, °C (time, h)	yield,[a] %	configuration of *endo*-**2**	endo (% ee):exo (% ee)[b]
1	**1a**	none	none	rt (5)	86		34:66
2	**1a**	**3a**	$Cu(OTf)_2$	−85 (22)	63	(1*R*,2*S*,4*S*)	>95 (92):<5
3	**1a**	**3a**	$Cu(OTf)_2$	−55 (22)	66	(1*R*,2*S*,4*S*)	>95 (78):<5
4	**1a**	**3b**	$Cu(OTf)_2$	−55 (24)	85	(1*S*,2*R*,4*R*)	>95 (30):<5
5	**1a**	**4a**	$Cu(OTf)_2$	−60 (22)	10	(1*R*,2*S*,4*S*)	91 (32):9
6	**1a**	**4b**	$Cu(OTf)_2$	−60 (22)	8		>95 (0):<5
7	**1a**	**5**	$Cu(OTf)_2$	−55 (22)	42	(1*R*,2*S*,4*S*)	80 (12):20 (0)
8	**1a**	**3a**	$Cu(SbF_6)_2$	−55 (22)	50	(1*R*,2*S*,4*S*)	>95 (30):<5
9	**1a**	**3a**	$Zn(OTf)_2$	−85 (22)	68	(1*R*,2*S*,4*S*)	>95 (90):<5
10	**1a**	**3a**	$Zn(OTf)_2$	−55 (22)	62	(1*R*,2*S*,4*S*)	>95 (67):<5
11	**1b**	none	none	rt (3)	90		67:33
12	**1b**	**3a**	$Cu(OTf)_2$	−85 (14)	85	(1*R*,2*S*,4*S*)	>95 (>98):<5
13	**1b**	**3a**	$Zn(OTf)_2$	−85 (22)	83	(1*R*,2*S*,4*S*)	>95 (>98):<5

[a] Isolated yield. [b] Endo:exo ratios were determined by ^{1}H NMR (400 MHz) on the crude product. The % ee was determined by chiral HPLC.

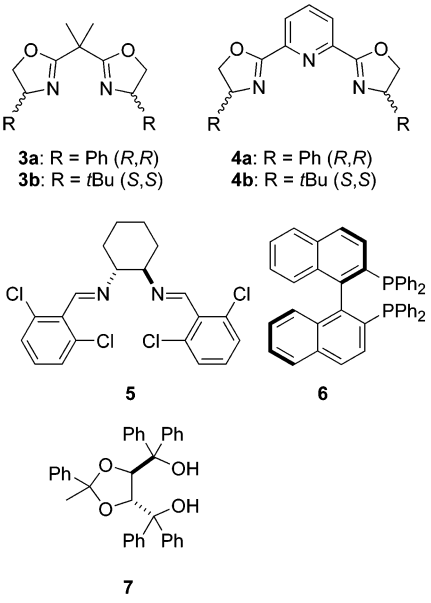
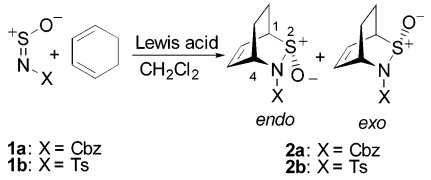


FIGURE 1. Chiral ligands.

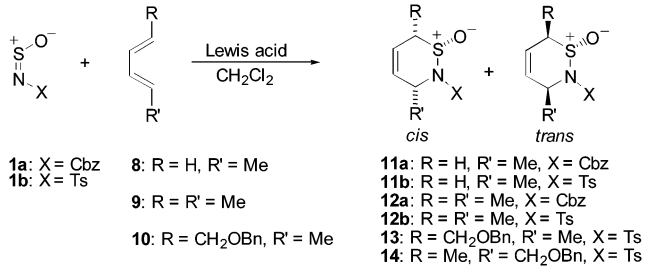
SCHEME 1. HDA Reactions of 1a and 1b with 1,3-Cyclohexadiene



up to 59% ee.[8,9] For **2a**, the exo selective thermal reaction (entry 1) became endo selective under the influence of the Lewis acids, while for **2b**, the Lewis acids reinforced the inherent endo selectivity of the thermal reaction (entry 11).

The **3a**−$Cu(OTf)_2$ and −$Zn(OTf)_2$ Lewis acids were further investigated in reactions of *N*-sulfinyl dienophiles **1a** and **1b** with dienes **8**−**10** (Scheme 2). Additionally,

SCHEME 2. HDA Reactions of 1a and 1b with Acyclic Dienes



the performance of the copper(II) and zinc(II) Lewis acids was compared to that of the Lewis acid generated from diol **7** and Me_2TiCl_2. The results are shown in Tables 2 and 3. As expected, reactions with the monosubstituted diene **8** provided exclusively the 3-substituted regioisomer.[12] Under the influence of the Lewis acids, reactions with dienes **8**−**10** afforded the cis isomer as the major compound. Again, the Lewis acid-promoted reaction of the *N*-sulfinylcarbamate **1a** (X = Cbz) had a cis/trans selectivity opposite to that of the thermal reaction, while for **1b** (X = Ts), the Lewis acid reinforced the inherent cis selectivity. Stoichiometric amounts of **3a**−$Cu(OTf)_2$ gave the best results, providing adducts **11a**, **11b**,[12c] **12a**,[3] and **12b**[13] in moderate to good enantioselectivities (61−97% ee), diastereoselectivities (80−90% de), and yields (57−68%) (Table 2, entries 2, 6, 10, and 14). Diene **10**[14] was applied in HDA reactions with *N*-sulfinyl dienophiles in order to test a diene containing an ether moiety. The HDA reaction of *N*-sulfinylsulfonamide **1b** and diene **10** leads to a mixture of regioisomers **13** and **14** (Scheme 2 and Table 3). The reaction is assumed to be cis selective both with and without Lewis acid. A similar reaction of (2*E*,4*E*)-1-benzyloxy-5-methyl-2,4-hexadiene with *N*-sulfinyl dienophile **1b** has been reported to provide a single

(10) For preparation of **7**, see: Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345. For a review on TADDOLs, see: Seebach, D.; Beck, A.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138.

(11) For preparation of Me_2TiCl_2, see: Clark, R. J. H.; Coles, M. A. *J. Chem. Soc., Dalton Trans.* **1974**, 1462−1467.

(12) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; p 1. (b) Levchenko, E. S.; Bal'on, Y. G.; Kisilenko, A. A. *Zh. Org. Khim.* **1965**, *1*, 155−159. (c) Kresze, G.; Wagner, U. *Liebigs Ann. Chem.* **1972**, *762*, 93−105. (d) Carpanelli, C.; Galani, G. *Gazz. Chim. Ital.* **1982**, *112*, 187−190.

(13) Mock, W. L.; Nugent, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 6521−6529.

(14) Li, Z.-H.; Wang, T.-S.; Yao, E.-Y.; Gao, Z.-H. *Chin. J. Chem.* **1990**, *3*, 265−270.

TABLE 2. HDA Reactions with Acyclic Dienes 8 and 9

entry	dienophile	diene	Lewis acid (100 mol %)	*T*, °C (time, h)	yield,[a] %	configuration of cis	cis (% ee):trans (% ee)
1	**1a**	**8**	none	rt (22)	92		10:90
2	**1a**	**8**	**3a**−$Cu(OTf)_2$	−45 (24)	60	(1*S*,3*R*)	>95 (77):<5
3	**1a**	**8**	**3a**−$Zn(OTf)_2$	−45 (22)	27	(1*S*,3*R*)	87 (58):13 (15)
4	**1a**	**8**	**7**−$TiCl_2$	−45 (20)	42	(1*S*,3*R*)	88 (22):12 (15)
5	**1b**	**8**	none	rt (22)	88		80:20
6	**1b**	**8**	**3a**−$Cu(OTf)_2$	−85 (22)	68	(1*S*,3*R*)	73 (87):27 (98)
7	**1b**	**8**	**3a**−$Zn(OTf)_2$	−85 (23)	20	(1*S*,3*R*)	>95 (50):<5 (79)
8	**1b**	**8**	**7**−$TiCl_2$	−85 (22)	37		80 (0):20
9	**1a**	**9**	none	rt (18)	75		18:82
10	**1a**	**9**	**3a**−$Cu(OTf)_2$	−45 (24)	57	(1*S*,3*R*,6*S*)	>95 (61):<5
11	**1a**	**9**	**3a**−$Zn(OTf)_2$	−45 (22)	41	(1*S*,3*R*,6*S*)	>95 (58):<5
12	**1a**	**9**	**7**−$TiCl_2$	−45 (20)	67	(1*R*,3*S*,6*R*)	88 (7):12 (33)
13	**1b**	**9**	none	rt (15)	84[b]		86:14
14	**1b**	**9**	**3a**−$Cu(OTf)_2$	−85 (25)	68[b]	(1*S*,3*R*,6*S*)	>95 (97):<5
15	**1b**	**9**	**3a**−$Zn(OTf)_2$	−85 (22)	19[b]	(1*S*,3*R*,6*S*)	>95 (26):<5
16	**1b**	**9**	**7**−$TiCl_2$	−50 (20)	65[b]	(1*S*,3*R*,6*S*)	78 (16):22 (13)

[a] Isolated yield. [b] Yield determined by ^{1}H NMR after flash chromatography.

TABLE 3. Reactions of 1b and 10 Promoted by Stoichiometric Amounts of Lewis Acids at −45 °C for 24 h

entry	Lewis acid	yield,[a] % (cis)	*cis*-**13** (% ee):**14** (% ee)[b]	yield,[a] % (trans)	*trans*-**13** (% ee):**14** (% ee)[b]
1[c]	none	86	69:31	13	89:11
2	**3a**−$Cu(OTf)_2$	31	>95 (65):<5	14	91 (84):9
3	**7**−$TiCl_2$	35	72 (25):28 (26)	14	>95 (71):<5

[a] Isolated yield. [b] The regioisomers **13** and **14** were not able to be separated by flash chromatography. A ratio of **13**:**14** was determined by ^{1}H NMR after flash chromatography. [c] Reaction at room temperature.

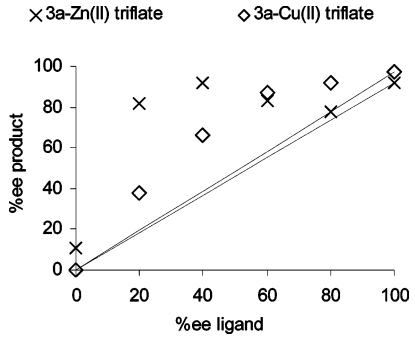


FIGURE 2. Investigation of nonlinear effects for the HDA reaction of **1a** and 1,3-cyclohexadiene promoted by **3a**−$Cu(OTf)_2$ and −$Zn(OTf)_2$, respectively.

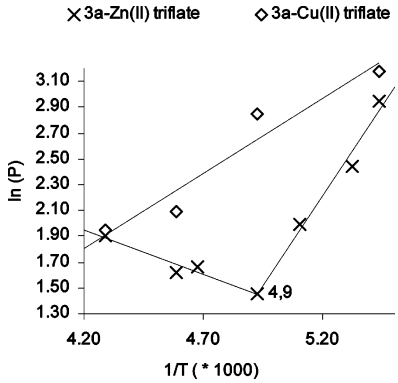


FIGURE 3. Eyring plots for the HDA reaction of **1a** and 1,3-cyclohexadiene promoted by **3a**−$Cu(OTf)_2$ and −$Zn(OTf)_2$, respectively.

regioisomer corresponding to **14**,[15] while chiral (3*E*)-5-benzyloxy-1,3-hexadiene derivatives gave a single regioisomer corresponding to *cis*-**13**.[16] Again, complex **3a**−$Cu(OTf)_2$ was the Lewis acid of choice providing *cis*- and *trans*-**13** with 65 and 84% ee, respectively (Table 3).

Mechanistic Aspects of Diels−Alder Reactions Promoted by 3a−Cu(II) and −Zn(II) Lewis Acids. Nonlinear Effects with Copper(II) and Zinc(II) Lewis Acids. The relationship between the enantiomeric excess of chiral ligand **3a** and the product was investigated for the reaction of *N*-sulfinylcarbamate **1a** and 1,3-cyclohexadiene catalyzed by stoichiometric amounts of **3a**−$Cu(OTf)_2$ and −$Zn(OTf)_2$ (Figure 2). In both systems, a precipitate was formed when the Lewis acids were prepared using partially resolved chiral ligands. A positive nonlinear effect[17] was observed for both catalysts, but the deviation from linearity was more pronounced for the zinc catalyst. This indicates that the active catalysts are formed as dimers or higher aggregated complexes. Moreover, the heterochiral catalysts were less active than the homochiral catalyst. In contrast to our observations, Evans et al. found linear relationships in **3a**−$Cu(SbF_6)_2$-catalyzed HDA and ene reactions.[22f] At the same time, the formation of a 2:1 ligand−metal complex of **3a** and $Cu(OTf)_2$ has been reported.[22f]

Temperature Dependence with 3a−Copper(II) and −Zinc(II) Lewis Acids. We have also studied the temperature dependence of the enantiomeric excess in the **3a**−$Cu(OTf)_2$ and −$Zn(OTf)_2$-catalyzed reactions of **1a** and 1,3-cyclohexadiene (Figure 3). For the copper catalyst, the Eyring plot showed a linear relationship within the investigated temperature range in accordance with reports by Evans' group.[22f] However, the zinc

(15) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087−3128.
(16) Hamada, T.; Sato, H.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1989**, *30*, 6405−6408.
(17) Guilaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439. (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959.

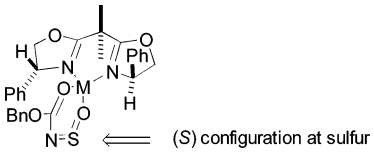


FIGURE 4. Postulated intermediate with tetrahedral arrangement.

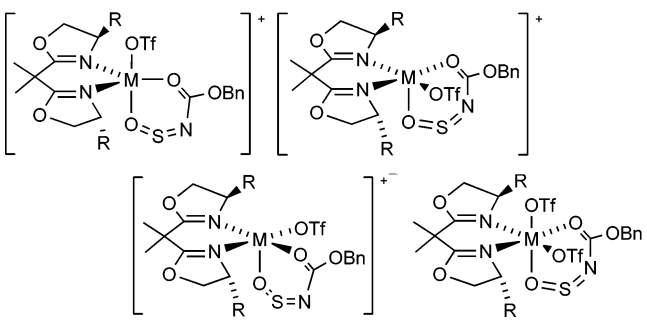
catalyst gave two lines with an inversion point at −70 °C (T^{-1} = 4.9 × 10^{-3}), indicating that two or more selective steps were involved in the reaction process.[18]

Stereochemical Model. The absolute configurations of the cycloadducts *endo*-**2a**, *endo*-**2b**, *cis*-**11a**, *cis*-**11b**, *trans*-**11b**, *cis*-**12a**, and *cis*-**12b**, obtained from reactions promoted by **3a**−$Zn(OTf)_2$ or −$Cu(OTf)_2$, were determined (as described below). All thiazine oxides had the *S* configuration at sulfur, implying that all dienes approach dienophiles **1a** and **1b** from the same side. Moreover, the orientation of the dienes toward the dienophiles in the Lewis acid-catalyzed reactions seemed to be controlled by secondary orbital interactions between the S=O bond and the diene. The postulated intermediate presented in Figure 4 is based on the assumption that *N*-sulfinyl dienophile **1a** or **1b** (last compound is not shown) engages in a bidentate coordination to the chiral Lewis acid with the sulfinyl oxygen and the carbonyl oxygen or one of the sulfonyl oxygens, respectively. Zhang and Flann suggested recently such a six-membered (O,O) chelate for the adduct of *N*-sulfinylphosphoramidates (X = $R_2O(O)P$) and $SnCl_4$ based on NMR and elemental analysis of the complex.[19] A tetrahedral metal center (Figure 4) or stereochemically equivalent geometries[20] explain the enantiofacial selectivity of the reactions shown in Tables 1 and 2. Tetrahedral metal center geometries have been found to be consistent with the stereochemical outcome of several HDA and ene reactions mediated by **3a**−zinc(II)[21] and −copper(II)[22] Lewis acids. Tetracoordinated zinc(II) complexes are commonly tetrahedral, while tetracoordinated copper(II) complexes are square planar; however, tetrahedral arrangements are rare.[23] Evans et al. argued for a distorted square planar arrangement of the bis(oxazoline) and the bidentate substrate in copper(II) complexes,[24] which have been supported by ESR studies[25] of **3b**−$Cu(OTf)_2$ in the presence of methyl pyruvate and X-ray crystallography of several bis(aquo)[22f,26] and substrate bis(oxazoline)−copper(II) complexes.[27] However, this model predicts the opposite absolute configuration of the products shown in Table 1. Jørgensen et al. reported similar inconsistencies between absolute configurations predicted from a model with a square planar copper center and experimental results for HDA and ene reactions with glyoxylate esters catalyzed by **3a**−copper(II) salts.[22a,b,d] A change in metal geometry from square planar to tetrahedral was proposed to explain the stereochemical outcome of the reactions. Nevertheless, structural and mechanistic studies done by Evans' group raised doubts that a tetrahedral geometry at the metal center is responsible for the reversal in enantioselectivity.[22f] Lately, Evans et al. proposed a trigonal pyramidal geometry, which occurs more frequently for tetracoordinated copper(II) complexes than for tetrahedral geometries.[22c,23]

Catalytic Reactions. When catalytic amounts (10 mol %) of the Lewis acids were used, the **3a**−$Cu(OTf)_2$ afforded low selectivities for the test reactions shown in Scheme 1 (Table 4; entry 3 for **1a** and entry 10 for **1b**). Better results were obtained with **3a**−$Zn(OTf)_2$ (entries 6 and 12). Unfortunately, the yields and stereoselectivities decreased compared to those of the reactions with stoichiometric amounts of the catalysts, presumably due to a nonselective background reaction (Table 4, entries 1 and 8) and an insufficient release of the catalyst from the HDA adducts.

The use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as an additive in combination with **3b**−$Cu(OTf)_2$ has previously been reported by Evans et al. in the catalytic enantioselective aldol additions of enol silans to pyruvate esters.[25b] To our great satisfaction, a significant improvement of the turnover as well as the diastereomeric excess and enantiomeric excess values was observed when TMSOTf (100 mol %) was used as an additive. Under these conditions, the copper and zinc catalysts behaved in a complementary manner. The best results for **1a** were obtained with 10 mol % ent-**3a**−$Cu(OTf)_2$ (ent = enantiomer), giving a 68% yield of *endo*-**2a**

(18) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem.* **1991**, *103*, 480−518.
(19) Zhang, Y.; Flann, C. J. *J. Org. Chem.* **1998**, *63*, 1372−1378.
(20) For example:



(21) Evans, D. A.; Kozolowski; M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484. (b) Yao, S.; Johannesen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2345−2349. For radical addition reactions, see: (c) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029−11030. (d) Bandini, M.; Cozzi, P. G.; de Angelis, M.; Umani-Ronchi, A. *Tetrahedron Lett.* **2000**, *41*, 1601−1605.
(22) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (b) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Chem. Commun.* **1997**, 2169−2170. (c) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825. (d) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117−1122. (e) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599−8605. (f) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879−2882. (g) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. (h) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. (i) Zhuang, W.; Thorhauge, J.; Jørgensen, K. A. *Chem. Commun.* **2000**, 459−460.
(23) Cambridge Structural Database survey (http://sulfur.scs.uiuc.edu/Intro%20Page/periodictable/pte.html).
(24) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.
(25) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699.
(26) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573.
(27) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995. (b) Audrian, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487−4497.

TABLE 4. Comparison of Catalytic HDA Reactions of 1a or 1b with 1,3-Cyclohexadiene with and without TMSOTf as an Additive

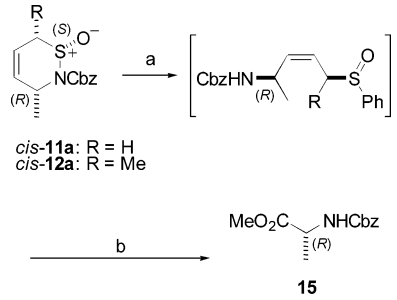
entry	dienophile	ligand	metal[c]/additive[d]	*T*, °C (time, h)	yield,[a] %	configuration of *endo*-**2**	endo (% ee):exo (% ee)[b]
1	**1a**	none	none	−55 (24)	17		14:86
2	**1a**	none	none/TMSOTf	−75 (22)	10		33:67
3	**1a**	**3a**	$Cu(OTf)_2$	−55 (22)	25	(1*R*,2*S*,4*S*)	38 (15):62 (0)
4	**1a**	ent-**3a**	$Cu(OTf)_2$/TMSOTf	−75 (22)	85	(1*S*,2*R*,4*R*)	>95 (96):<5
5	**1a**	ent-**3a**	$Cu(OTf)_2$/TMSOTf	−75 (4)	68	(1*S*,2*R*,4*R*)	>95 (98):<5
6	**1a**	**3a**	$Zn(OTf)_2$	−75 (22)	30	(1*R*,2*S*,4*S*)	75 (61):25 (0)
7	**1a**	ent-**3a**	$Zn(OTf)_2$/TMSOTf	−75 (22)	70	(1*S*,2*R*,4*R*)	92 (86):8
8	**1b**	none	none	−85 (17)	55		64:36
9	**1b**	none	none/TMSOTf	−75 (22)	71		71:29
10	**1b**	**3a**	$Cu(OTf)_2$	−85 (24)	93	(1*R*,2*S*,4*S*)	82 (36):18 (0)
11	**1b**	ent-**3a**	$Cu(OTf)_2$/TMSOTf	−75 (22)	56	(1*S*,2*R*,4*R*)	92 (80):8
12	**1b**	**3a**	$Zn(OTf)_2$	−75 (22)	39	(1*R*,2*S*,4*S*)	92 (78):8
13	**1b**	ent-**3a**	$Zn(OTf)_2$/TMSOTf	−75 (22)	86	(1*S*,2*R*,4*R*)	>95 (97):<5
14	**1b**	ent-**3a**	$Zn(OTf)_2$/TMSOTf	−75 (4)	83	(1*S*,2*R*,4*R*)	>95 (96):<5

[a] Isolated yield. [b] Endo:exo ratio was determined by ^{1}H NMR (400 MHz) on the crude product. The % ee was determined by chiral HPLC. [c] Reaction with 10 mol %. [d] Reaction with 100 mol %.

(98% ee; entry 5). For **1b**, ent-**3a**−$Zn(OTf)_2$ gave 86% yield of *endo*-**2b** (97% ee; entry 13). Since TMSOTf itself is known to exhibit Lewis acid properties,[28] test reactions were run with TMSOTf as the only promoter present (entries 2 and 9). Although minor differences were observed compared to the background reactions (entries 1 and 8), no major improvements of yields or endo:exo ratios were obtained. Thus, the combination of the chiral catalysts and the additive is essential for optimal results. The TMSOTf is assumed to assist the release of the chiral catalyst from the HDA adducts and thereby improve the catalytic turnover. Further studies of the mechanism, as well as the scope and limitations of TMSOTf as an additive, are currently in progress.

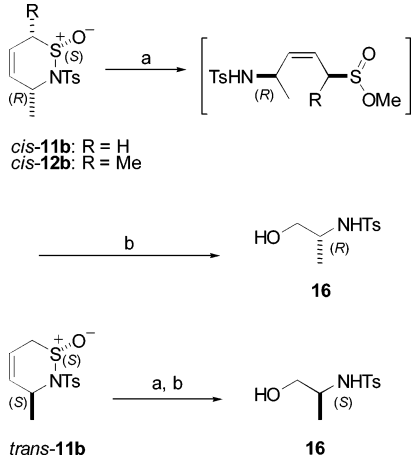
Configuration of the Diels−Alder Products. For the thiazine oxides **11a** (X = Cbz),[29a] **11b** (X = Ts),[29b] and **12b** (X = Ts),[29c] the orientation of the sulfoxide group relative to the methyl groups at the thiazine ring was determined by X-ray analyses, while the relative configuration of the thiazine oxide **12a** (X = Cbz) has been determined by others.[3] All thiazine oxides applied in the experiments described below were obtained from HDA reactions promoted by **3a**−$Zn(OTf)_2$ or −$Cu(OTf)_2$. The absolute configurations of the thiazine oxides **11a** and **12a** (X = Cbz) were determined by chemical correlation with alanine methyl ester **15**.[30] The cis isomers were treated with PhMgBr, followed by ozonolysis in methanolic NaOH[31] to yield the (*R*)-alanine methyl ester **15** in both cases (Scheme 3). Consequently, *cis*-**11a** had the (1*S*,3*R*) configuration, and *cis*-**12a** had the (1*S*,3*R*,6*S*) configuration. Surprisingly, we were not able to apply an analogous strategy to the thiazine oxides **11b** and **12b** (X = Ts). Thus, the absolute configuration of the cis isomers of **11b** and **12b** and the trans isomer of **11b** were determined by chemical correlation with the alaninol

SCHEME 3. Transformation of *N*-Cbz Thiazine Oxides to *N*-Cbz Alanine Methyl Ester[a]



[a] Reagents and conditions: (a) (1) PhMgBr, −60 °C, THF, (2) NH_4Cl; (b) O_3, −78 °C, NaOH/MeOH, CH_2Cl_2, 32% (from **11a**) and 37% (from **12a**).

SCHEME 4. Transformation of *N*-Ts Thiazine Oxides to *N*-Ts Alaninol[a]



[a] Reagents and conditions: (a) MeOH, room temperature (rt); (b) (1) O_3, −78 °C, MeOH, (2) $NaBH_4$, 56−57% (from **11b**) and 82% (from **12b**).

16.[32] The thiazine oxides were stirred in MeOH before treatment with ozone and reductive workup with $NaBH_4$ (Scheme 4). The cis isomers of **11b** and **12b** provided the (*R*)-alaninol **16** and, thus, had the (1*S*,3*R*) and the

(28) Oishi, M. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 355−393.

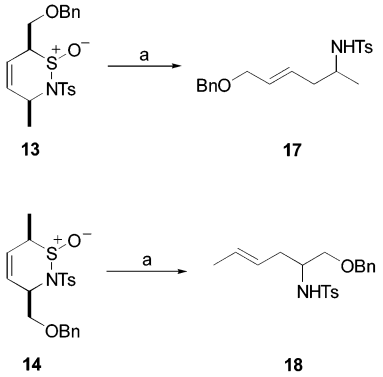
(29) Hansen, L. K.; Bayer, A.; Gautun, O. R. *Acta Crystallogr.* **2002**, *E58*, o165−o166. (b) Hansen, L. K.; Bayer, A.; Gautun, O. R. *Acta Crystallogr.* **2001**, *E57*, o1109−o1110. (c) Hansen, L. K.; Bayer, A.; Gautun, O. R. *Acta Crystallogr.* **2002**, *E58*, o198−o199.

(30) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560−565. (b) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962−1965. (c) Huneck, S.; Porzel, A. *Z. Naturforsch., B: Chem. Sci.* **1994**, *49*, 569−575.

(31) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675−3680.

(32) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517−5518.

SCHEME 5. Transformation of *N*-Ts Thiazine Oxides 13 and 14 to Amino Alcohols 17 and 18, Respectively[a]



[a] Reagents and conditions: (a) (1) 5% NaOH, (2) 5% HCl, 53–58%.

(1*S*,3*R*,6*S*) configuration, respectively, while the trans isomer **11b** provided the (*S*)-alaninol and had the (1*S*,3*S*) configuration. The determination of the absolute configurations of thiazine oxides *endo*-**2** (X = Ts and Cbz) has been described elsewhere.[8,9] The major isomers of **13** and **14** were assumed to have the cis orientation of the S=O bond relative to the other ring substituents. This assumption was based on the general trend for *N*-sulfinyl compound **1b** to provide the cis adducts as major products in the HDA reaction. The ^{1}H NMR shifts of **13** (1.35 ppm) with the protons of the Me substituents at the 3-position for *cis*-**11b** (1.34 ppm) and *cis*-**12b** (1.30 ppm) corresponded well. These chemical shifts are upfield from those protons in the minor *trans*-**11b** (1.46), *trans*-**12b** (1.45 ppm), and minor **13** (1.42 ppm). A similar comparison of the chemical shifts for the Me groups in the 6-positions in **12b** and **14** identified *cis*-**14** as the major isomer. More support was obtained from the coupling patterns in the alkene region of ^{1}H NMR spectra. In general, we observed that HDA adducts with a cis orientation of the S=O bound alkene protons appear as a double of triplets (dt), while in trans adducts, the alkene protons appear as a double of doublets (dd).

The regioselectivity in the HDA reaction of monosubstituted diene **8** was established by ^{1}H,^{1}H correlated NMR of cycloadduct **11**. Regioisomers **13** and **14** were identified by the chemical transformation into the protected amino alcohols **17** and **18**, respectively (Scheme 5), which were characterized by ^{1}H,^{1}H correlated NMR. Mixtures of thiazine oxides **13** and **14** were treated with 5% aqueous NaOH followed by 5% aqueous HCl. A mixture of cis isomers (**13**:**14** = 2.2:1) and a mixture of trans isomers (**13**:**14** = 8.3:1) provided the amino alcohol **17** as the major product. Thus, regioisomer **13** was the major product in the Diels–Alder reaction of diene **10** and *N*-sulfinyl dienophile **1b**.

Conclusion

In conclusion, asymmetric hetero-Diels–Alder reactions of *N*-sulfinyl dienophiles using bis(oxazoline)–copper(II) and –zinc(II) triflates have been presented. A range of dienes can be employed using stoichiometric amounts of the catalyst to provide the cycloadducts in good enantioselectivities, diastereoselectivities, and yields. The configuration of several cycloadducts has been determined and can be explained by a stereochemical model proposing a tetrahedral metal center. Positive nonlinear effects indicated the presence of heterochiral species catalytically less active than the homochiral catalyst. Investigations of the temperature dependence of the enantioselectivity revealed that at least two selective reaction paths exist in the zinc-catalyzed reaction. Reactions run with catalytic amounts of chiral Lewis acids gave low yields and selectivities. However, with addition of TMSOTf (100 mol %) to these systems, excellent yields and enantioselectivities were obtained.

Experimental Section

General Catalyst Preparation. Preparation of the Zinc(II)–Bis(oxazoline) Catalyst [3a–Zn(OTf)$_2$]. An oven-dried round-bottom flask was charged with zinc triflate (14.3 mg, 0.039 mmol) under an argon atmosphere. Dry CH_2Cl_2 (1 mL) and a solution of bis(oxazoline) **3a** in CH_2Cl_2 (0.5 M, 1.05 equiv) were added, and the resulting suspension was stirred for 3 h. At this time, most of the solids had dissolved.

General Procedure for the Asymmetric HDA Reactions Using 100 mol % Catalyst. A solution of the catalyst was cooled to –85 °C before a solution of *N*-sulfinyl compound **1** in CH_2Cl_2 (Ts 0.5 M; Cbz 1.0 M, 0.40 mmol) was added. The resulting mixture was stirred for 10 min before a precooled solution of the diene (1.5–2.5 equiv) in CH_2Cl_2 (1 mL) was added. Occasionally, the diene was added slowly along the wall of the flask. After the appropriate reaction time, the reaction mixture was quenched by the addition of a phosphate buffer (pH 7, 3 mL), allowed to warm to room temperature, and extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and, thereafter, purified by FC. The enantiomeric composition was determined by chiral HPLC.

HDA Reactions for the Investigation of the Nonlinear Effect (Stoichiometric Amount Catalyst). The catalysts in different enantiomeric compositions were prepared according to the procedure described above. The scalemic mixtures of the bis(oxazoline) ligand were obtained by mixing **3a** (0.5 M in CH_2Cl_2) and ent-**3a** (ent = enantiomer; 0.5 M in CH_2Cl_2) under an argon atmosphere before addition. The HDA reactions were performed as described in the typical procedure.

General Procedure for the Asymmetric HDA Reactions Using 10 mol % Catalyst. A solution of the *N*-sulfinyl compound **1** (620 μL, 0.4 M in CH_2Cl_2, 0.248 mmol) was added into the precooled solution of the catalyst at –75 °C. A precooled solution of 1,3-cyclohexadiene (2.5 equiv) in CH_2Cl_2 (500 μL) and TMSOTf (1 equiv) was added into the reaction mixture. The diene solution was added slowly along the wall of the round flask. The reaction mixture was stirred at –75 °C for 4–22 h and quenched by the addition of a phosphate buffer (pH 7, 4 mL). Then the reaction mixture was allowed to heat to room temperature and was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. The ^{1}H NMR of the crude product determined the diastereomeric ratio. The crude product was purified by FC and the enantiomeric composition determined by chiral HPLC.

Benzyl (1*S*,3*R*)-3,6-Dihydro-3-methyl-1λ^4,2-thiazine-2-carboxylate 1-Oxide (*cis*-11a). FC (Et_2O/pentane, 80/20) of the crude product afforded *cis*-**11a** as a white solid. Analytical data for *cis*-**11a**: mp 86–87 °C; $[\alpha]^{20}_D$ –7.7° (*c* 1.0, CH_2Cl_2); HPLC (Chiralpak AD, *i*PrOH/hexane, 20/80, 0.7 mL min^{-1}, 230 nm) 77% ee, t_R 11.3 (1*S*,3*R*) and 12.5 (1*R*,3*S*) min; ^{1}H NMR δ 7.40–7.31 (5H, m, Bn), 6.02 (1H, dt, *J* = 11.0, 2.7 Hz, 4H), 5.73 (1H, ddd, *J* = 11.0, 6.0, 2.9 Hz, 5H), 5.29 (1H, AB, *J* = 12.2 Hz, Bn), 5.24 (1H, AB, *J* = 12.2 Hz, Bn), 4.62–4.55 (1H,

m, 3H), 3.43−3.40 (2H, m, 6H), 1.48 (3H, d, J = 7.0 Hz, Me); ^{13}C NMR δ 153.5, 135.2, 130.7, 128.7, 128.6, 128.3, 112.0, 68.7, 49.8, 48.6, 22.2; IR (neat) ν 3034 (m), 2933 (m), 1713 (s), 1604 (w), 1496 (w), 1390 (s), 1299 (s), 1109 (s), 1087 (s); EIMS m/z (relative intensity) 265 (M^+, 0.8), 91 (100). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.63; H, 5.71; N, 5.15.

Benzyl (1*R,3*R**)-3,6-Dihydro-3-methyl-1λ^4,2-thiazine-2-carboxylate 1-Oxide (*trans*-11a).** FC (Et_2O/pentane, 80/20) of the crude product afforded *trans*-**11a** as colorless oil. Analytical data for *trans*-**11a**: HPLC (Chiralcel OJ, *i*PrOH/hexane, 60/40, 0.7 mL min^{-1}, 230 nm) t_R 12.0 and 20.5 min; ^{1}H NMR δ 7.41−7.33 (5H, m, Bn), 6.37 (1H, ddd, J = 9.8, 6.2, 2.9 Hz, 4H), 5.86 (1H, ddd, J = 9.8, 7.4, 2.9 Hz, 5H), 5.31 (1H, AB, J = 12.2 Hz, Bn), 5.24 (1H, AB, J = 12.2 Hz, Bn), 4.62 (1H, pent, J = 6.2 Hz, 3H), 3.52 (1H, dAB, J = 15.3, 7.5 Hz, 6H), 3.40 (1H, mAB, J = 15.3 Hz, 6H), 1.35 (3H, d, J = 6.2 Hz, Me); ^{13}C NMR δ 154.7, 135.3, 134.4, 128.7, 128.5, 128.2, 114.2, 69.0, 50.2, 47.2, 20.2; IR (KBr tablet) ν 3032 (m), 2971 (m), 2931 (m), 1713 (s), 1497 (m), 1454 (m), 1384 (s), 1283 (s), 1097 (s), 1065 (s); EIMS m/z (relative intensity) 265 (M^+, 0.6), 91 (100). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.67; H, 5.83; N, 5.41.

(1*S*,3*R*)-3,6-Dihydro-3-methyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*cis*-11b).[12c] FC (Et_2O/pentane, 90/10) of the crude product afforded *cis*-**11b** as a white solid. Analytical data for *cis*-**11b**: $[\alpha]^{20}_D$ +4.7° (c 1.0, CH_2Cl_2); HPLC (Chiralcel OJ, *i*PrOH/hexane, 35/65, 0.7 mL min^{-1}, 230 nm) 54% ee, t_R 22.7 (1*S*,3*R*) and 36.5 (1*R*,3*S*) min; ^{1}H NMR δ 7.81 (2H, d, J = 8.4 Hz, Ts), 7.34 (2H, d, J = 8.1 Hz, Ts), 5.97 (1H, dt, J = 11, 3 Hz, 4H), 5.75−5.67 (1H, m, 5H), 4.62−4.55 (1H, m, 3H), 3.45 (1H, dd, J = 16.5, 6.6 Hz, 6H), 3.38−3.30 (1H, m, 6H), 2.43 (3H, s, Ts), 1.34 (3H, d, J = 7.0 Hz, Me); ^{13}C NMR δ 144.8, 137.5, 130.5, 130.2, 127.2, 112.6, 51.1, 49.5, 22.3, 21.7; IR (KBr tablet) ν 3030 (m), 2935 (m), 1598 (m), 1496 (w), 1334 (s), 1162 (s), 1092 (s); EIMS m/z (relative intensity) 265 (M^+, 3), 91 (100). Anal. Calcd for $C_{12}H_{15}NO_3S_2$: C, 50.51; H, 5.30; N, 4.91. Found: C, 50.25; H, 5.57; N, 4.80. A racemic sample, (1*R**,3*S**)-**11b**, recrystallized from CH_2Cl_2/heptane melted at 138−139 °C (lit. 142 °C).[12c]

(1*R,3*R**)-3,6-Dihydro-3-methyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*trans*-11b).**[12c] FC (Et_2O/pentane, 90/10) of the crude product afforded *trans*-**11b** as a colorless viscous oil. Analytical data for *trans*-**11b**: HPLC (Chiralcel OJ, *i*PrOH/hexane, 35/65, 0.7 mL min^{-1}, 230 nm) t_R 22.0 (1*R*,3*R*) and 25.7 (1*S*,3*S*) min; ^{1}H NMR δ 7.88 (2H, d, J = 8.4 Hz, Ts), 7.32 (2H, d, J = 8.4 Hz, Ts), 6.05 (1H, ddd, J = 10.2, 4.8, 2.6 Hz, 4H), 5.75 (1H, m, 5H), 4.04−3.95 (1H, m, 3H), 3.58−3.53 (2H, m, 6H), 2.43 (3H, s, Ts), 1.46 (3H, d, J = 6.6 Hz, Me); ^{13}C NMR δ 144.9, 134.5, 133.6, 130.0, 128.4, 113.7, 50.8, 49.1, 21.7, 20.8.

Benzyl (1*S*,3*R*,6*S*)-3,6-Dihydro-3,6-dimethyl-1λ^4,2-thiazine-2-carboxylate 1-Oxide (*cis*-12a).[3] FC (Et_2O/pentane, 60/40) of the crude product afforded *cis*-**12a** as a white solid. Analytical data for *cis*-**12a**: $[\alpha]^{20}_D$ −15° (c 1, CH_2Cl_2); HPLC (Chiralcel OJ, *i*PrOH/hexane, 20/80, 0.7 mL min^{-1}, 230 nm) 61% ee, t_R 20.1 (1*R*,3*S*,6*R*) and 22.7 (1*S*,3*R*,6*S*) min; ^{1}H NMR δ 7.40−7.29 (5H, m, Bn), 5.93 (1H, dt, J = 11.0, 2.9 Hz, 4H), 5.40 (1H, dt, J = 11.0, 2.4 Hz, 5H), 5.28 (1H, AB, J = 12.2 Hz, Bn), 5.24 (1H, AB, J = 12.2 Hz, Bn), 4.55−4.48 (1H, m, 3H), 3.37−3.29 (1H, m, 6H), 1.45 (3H, d, J = 7.0 Hz, Me), 1.44 (3H, d, J = 7.0 Hz, Me); ^{13}C NMR δ 153.5, 135.3, 130.3, 128.62, 128.61, 128.3, 119.2, 68.7, 52.1, 49.6, 22.3, 15.8; EIMS m/z (relative intensity) 279 (M^+, 5), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.42; H, 6.20; N, 4.94. A racemic sample melted at 79−81 °C.

Benzyl (1*R,3*R**,6*S**)-3,6-Dihydro-3,6-dimethyl-1λ^4,2-thiazine-2-carboxylate 1-Oxide (*trans*-12a).**[3] FC (Et_2O/pentane, 80/20) of the crude product afforded *trans*-**12a** as a colorless oil. Analytical data for *trans*-**12a**: HPLC (Chiralcel OJ, *i*PrOH/hexane, 40/60, 0.7 mL min^{-1}, 230 nm) t_R 13.2 and 14.6 min; ^{1}H NMR δ 7.41−7.31 (5H, m, Bn), 6.09 (1H, dd, J = 10.6, 4.8 Hz, 4H), 5.85 (1H, dd, J = 10.6, 7.0 Hz, 5H), 5.27 (2H, s, Bn), 4.41 (1H, m, 3H), 3.45 (1H, m, 6H), 1.48 (3H, d, J = 6.2 Hz, 3Me), 1.35 (3H, d, J = 7.3 Hz, 6Me); ^{13}C NMR δ 155.8, 135.3, 132.2, 128.7, 128.5, 128.1, 119.1, 69.0, 54.1, 49.2, 22.2, 16.6; IR (KBr tablet) ν 3034 (w), 2973 (m), 2931 (m), 1723 (s), 1497 (w), 1273 (s), 1244 (s), 1104 (s); EIMS m/z (relative intensity) 279 (M^+, 0.4), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 59.89; H, 6.40; N, 4.90.

(1*R,3*S**,6*R**)-3,6-Dihydro-3,6-dimethyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*cis*-12b).**[13] FC (Et_2O/pentane, 60/40) of the crude product provided a mixture of *cis*-**12b** and *p*-toluenesulfonamide. All attempts to separate these compounds failed. Data for *cis*-**12b**: HPLC (Chiralcel OJ, *i*PrOH/hexane, 60/40, 0.7 mL min^{-1}, 230 nm) t_R 13.7 (1*S*,3*R*,6*S*) and 19.0 (1*R*,3*S*,6*R*) min; ^{1}H NMR δ 7.82 (2H, d, J = 8.4 Hz, Ts), 7.34 (2H, d, J = 8.1 Hz, Ts), 5.88 (1H, dt, J = 11.0, 3.3 Hz, 4H), 5.40 (1H, dt, J = 11.0, 2.0 Hz, 5H), 4.59−4.51 (1H, m, 3H), 3.33−3.25 (1H, m, 6H), 2.43 (3H, s, Me), 1.43 (3H, d, J = 7.3 Hz, 6Me), 1.30 (3H, d, J = 7.0 Hz, 3Me); ^{13}C NMR δ 144.7, 137.7, 130.2, 129.9, 127.2, 119.7, 53.4, 50.9, 22.3, 21.7, 15.8.

(1*R,3*R**,6*S**)-3,6-Dihydro-3,6-dimethyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*trans*-12b).**[13] FC (Et_2O/pentane, 90/10) of the crude product afforded *trans*-**12b** as a white solid. Analytical data for *trans*-**12b**: mp 136−137 °C (rac); HPLC (Chiralpak AD, *i*PrOH/hexane, 50/50, 0.7 mL min^{-1}, 230 nm) t_R 10.7 and 24.2 min; ^{1}H NMR δ 7.85 (2H, d, J = 8.1 Hz, Ts), 7.34 (2H, d, J = 8.1 Hz, Ts), 5.80−5.72 (2H, m, 4/5H), 3.90−3.84 (1H, m, 3H), 3.49−3.42 (1H, m, 6H), 2.42 (3H, s, Me), 1.45 (3H, d, J = 6.6 Hz, 3Me), 1.38 (3H, d, J = 7.0 Hz, 6Me); ^{13}C NMR δ 144.9, 134.8, 131.5, 130.1, 128.2, 119.5, 55.8, 49.6, 21.7, 21.2, 17.0; IR (KBr tablet) ν 3034 (w), 2973 (m), 2931 (m), 1495 (m), 1496 (w), 1346 (s), 1166 (s); EIMS m/z (relative intensity) 299 (M^+, 0.3), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_3S_2$: C, 52.15; H, 5.72; N, 4.68. Found: C, 52.40; H, 5.48; N, 4.62.

(1*R,3*S**,6*R**)-3,6-Dihydro-6-[(benzyloxy)methyl]-3-methyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*cis*-13) and (1*R**,3*S**,6*R**)-3,6-Dihydro-3-[(benzyloxy)methyl]-6-methyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*cis*-14).** FC (EtOAc/pentane, 50/50) provided an inseparable mixture of *cis*-**13** and *cis*-**14** as a pale yellow oil. TLC R_f = 0.56 (EtOAc/pentane, 50/50). Anal. Calcd of the mixture $C_{20}H_{23}NO_4S_2$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.40; H, 6.01; N, 3.26. Data for *cis*-**13**: HPLC (Chiralpak AD, *i*PrOH/hexane, 20/80, 0.5 mL min^{-1}, 230 nm) t_R 38.3 and 46.2 min; ^{1}H NMR δ 7.82 (2H, d, J = 8.4 Hz, Ts), 7.37−7.23 (7H, m, Ts/Ph), 5.91 (1H, dt, J = 11.0, 3.3 Hz, 4H), 5.28 (1H, dt, J = 11.0, 2.2 Hz, 5H), 4.63 (1H, AB, J = 12.1 Hz, Bn), 4.52 (1H, AB, J = 12.1 Hz, Bn), 4.62−4.56 (1H, m, 3H), 3.72 (2H, d, J = 8.4 Hz, CH_2), 3.53−3.47 (1H, m, 6H), 2.43 (3H, s, Ts-Me), 1.35 (3H, d, J = 7.0 Hz, Me); ^{13}C NMR δ 144.7, 137.6, 137.3, 130.8, 130.2, 128.6, 127.9, 127.2, 114.5, 73.7, 68.5, 60.5, 51.8, 22.5, 21.7. Data for *cis*-**14**: HPLC (Chiralpak AD, *i*PrOH/hexane, 20/80, 0.7 mL min^{-1}, 230 nm) t_R 21.6 and 22.9 min; ^{1}H NMR δ 7.73 (2H, d, J = 6.6 Hz, Ts), 7.37−7.23 (7H, m, Ts/Ph), 6.16 (1H, dt, J = 11.0, 3.3 Hz, 4H), 5.43 (1H, dt, J = 11.0, 2.2 Hz, 5H), 4.69−4.60 (1H, m, 3H), 4.44 (1H, AB, J = 12.1 Hz, Bn), 4.36 (1H, AB, J = 12.1 Hz, Bn), 3.54 (2H, d, J = 8.9 Hz, CH_2), 3.28−3.24 (1H, m, 6H), 2.41 (3H, s, Ts-Me), 1.42 (3H, d, J = 7.3 Hz, Me); ^{13}C NMR (selected signals) δ 144.7, 137.9, 130.1, 128.5, 128.1, 127.7, 126.0, 120.6, 72.5, 53.1, 15.7.

(1*R,3*R**,6*S**)-3,6-Dihydro-6-[(benzyloxy)methyl]-3-methyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*trans*-13) and (1*R**,3*R**,6*S**)-3,6-Dihydro-3-[(benzyloxy)methyl]-6-methyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (*trans*-14).** FC (EtOAc/pentane, 50/50) provided an inseparable mixture of *trans*-**13** and *trans*-**14** as a white solid. TLC R_f = 0.29 (EtOAc/pentane, 50/50). Anal. Calcd of the mixture $C_{20}H_{23}NO_4S_2$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.07; H, 5.96; N, 3.18. Data for *trans*-**13**: HPLC (Chiralcel OJ, *i*PrOH/hexane, 60/40, 0.6 mL min^{-1}, 230 nm) t_R 35.6 and 44.6 min; ^{1}H NMR δ 7.84 (2H, d, J = 7.7 Hz, Ts), 7.40−7.25 (7H, m, Ts/Ph), 5.88 (1H, dd, J = 10.6, 3.2 Hz, 4H), 5.63 (1H, dd, J = 10.4, 6.7 Hz, 5H), 4.58 (1H, AB, J

= 11.9 Hz, Bn), 4.51 (1H, AB, J = 11.9 Hz, Bn), 3.98−3.92 (1H, m, 3H), 3.83−3.78 (1H, m, 6H), 3.68 (1H, m, CH_2), 3.56 (1H, m, CH_2), 2.42 (3H, s, Ts-Me), 1.42 (3H, d, J = 6.8 Hz, Me); ^{13}C NMR δ 144.8, 137.2, 135.1, 133.8, 129.9, 128.6, 128.0, 127.97, 127.6, 114.8, 73.5, 69.6, 62.0, 49.6, 21.6, 21.1. Data for *trans*-**14**: ^{1}H NMR (selected signals) δ 7.79 (2H, m, Ts), 7.18 (2H, m, Ts), 6.04 (1H, dd, J = 10.7, 3.5 Hz), 5.88 (1H, overlap), 4.35 (2H, AB, J_{AB} = 11.9 Hz, Bn), 2.40 (3H, s, Ts-Me); ^{13}C NMR δ 144.9, 137.6, 134.7, 130.8, 130.3, 129.7, 128.3, 127.8, 127.1, 121.0, 114.4, 73.1, 70.0, 55.7, 53.5, 22.4, 16.2.

Acknowledgment. We thank the Norwegian Research Council (Grant 122792/432 to A.B. and Grant 140593/431 to M.M.E.) for generous financial support.

Supporting Information Available: Stereochemical proofs by chemical correlation; experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0490245