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Catalytic Asymmetric Hetero Diels–Alder Reactions of *N*-Sulfinyl Dienophiles with Chiral Bis(oxazoline)copper(II) and -zinc(II) Triflates

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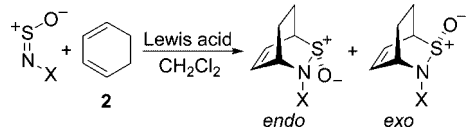
Asymmetric hetero Diels–Alder (HDA) reactions of *N*-sulfinyl dienophiles with bis(oxazoline)copper(II) and -zinc(II) triflates are described. The cycloaddition with cyclic and acyclic 1,3-dienes has been studied. The copper catalyst was found to be more efficient. With 10 mol-% of catalyst loading, a pronounced enhancement in turnover, diastereoselectivity (54–>90 % *de*), and enantioselectivity (30–98 % *ee*) was obtained by the addition of 100 mol-% of TMSOTf. The role of the additive is unclear, but we hypothesize that it is involved in the breakdown of catalyst-sulfine aggregates assists in the release of catalyst from the HDA adducts. Mechanistic studies revealed a positive nonlinear effect with the zinc catalyst, assumed to arise from the formation of less reactive heterochiral complexes. The copper catalyst showed a nearly linear relationship between the enantioselectivity of the ligand tested and the HDA product formed. The relative configurations and, in one case, the absolute configuration of the HDA products were established by X-ray analysis. Finally, an enantioselective route to (3a*R*,6a*S*)-3,3a,4,6a-tetrahydrocyclopenta[*d*][1,3]oxazol-2-one, a precursor of the C-ring in agelastatin A, applying the asymmetric HDA reaction is described.

Introduction

Hetero Diels–Alder (HDA) reactions of *N*-sulfinylaniline to conjugated dienes were first described by Wichterle and Rocek in 1953.[1] Since then, a number of Diels–Alder (DA) reactions for various types of *N*-sulfinyl compounds have been reported.[2] The resulting 1,2-thiazine 1-oxide adducts can be further transformed into synthetically useful derivatives including homoallylic amines and vicinal amino alcohols by well-established techniques.[2f] Only a few examples of asymmetric HDA reactions with either chiral *N*-sulfinyl dienophiles[3] or chiral dienes[4] have been reported to proceed with high diastereoselectivities (>97% *de*). The application of chiral Lewis-acid complexes as catalysts for DA and HDA reactions has been demonstrated to give excellent chiral induction for many different reaction systems.[5]

Recently, we described our preliminary findings with 10 mol-% of bis(oxazoline)copper(II) or zinc(II)[6] triflates in combination with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 100 mol-%) to catalyze asymmetric HDA reactions of *N*-sulfinyl dienophiles.[7a] The use of TMSOTf as an additive was crucial to obtain high yields (68–86%) and enantioselectivities (97–98% *ee*) for the applied test system shown in Scheme 1. TMSOTf was assumed to assist the release of the chiral catalyst from the HDA adducts and thereby, improve the catalytic turnover. Herein, we present further studies of this catalytic reaction including the effect of catalyst and TMSOTf loading, the use of other additives, non linear effects, and cycloaddition with cyclic and acyclic 1,3-dienes. Furthermore, an enantioselective route to (3a*R*,6a*S*)-3,3a,4,6a-tetrahydrocyclopenta[*d*][1,3]oxazol-2-one [(3a*R*,6a*S*)-**20**], a precursor of the C-ring in agelastatin A,[8] applying the asymmetric HDA reaction is presented.



Scheme 1. The test system: HDA reactions of *N*-sulfinyl dienophiles **1a** and **1b** with 1,3-cyclohexadiene (**2**).

Results and Discussion

Reaction Optimization

A series of chiral Lewis acids have previously been screened as promoters for the asymmetric HDA test reaction of *N*-sulfinyl dienophiles **1a**[9] and **1b**[2b] with 1,3-cyclohexadiene (**2**) shown in Scheme 1.[7] The best results were obtained with stoichiometric amounts of **4a**-Cu(OTf)$_2$ or **4a**-Zn(OTf)$_2$[10] (Figure 1), providing the *endo* adducts **3a**

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(X = Cbz) or **3b** (X = Ts) in good enantioselectivities (90–98% *ee*), diastereoselectivities (>90% *de*), and yields (63–85%).[7a,7b] Attempts to perform the test reactions with catalytic amounts of the Lewis acids gave rather disappointing results. A distinct drop in *de* and *ee* was observed in reactions with 10 mol-% loading of ent-**4a**-Cu(OTf)$_2$ (ent = enantiomer), as shown in Table 1, Entries 1 and 2 for *N*-sulfinyl **1a** and **1b**, respectively. Better results were obtained with ent-**4a**-Zn(OTf)$_2$ (Table 1, Entries 11 and 12), but the yields and stereoselectivities decreased compared to those of the reactions with stoichiometric amounts of the catalyst. The results indicate that the catalysts are not released from the HDA adducts, thus inhibiting the catalyst turnover. The high yield observed in the reaction with the Ts-containing dienophile **1b** (93%, Table 1, Entry 2) may be explained by a pronounced, competitive, uncatalyzed, HDA reaction. The uncatalyzed reaction at –85 °C (reaction time 17 h) gave a 55% yield of product **3b** (*endo*/*exo*, 64:36). For the Cbz-substituted dienophile **1a**, the uncatalyzed reaction gave a 17% yield of **3a** (*endo*/*exo*, 14:86) at –55 °C after 24 h.

Zhang and Flann recently suggested a six-membered (O,O) chelate for the adduct of *N*-sulfinylphosphoramidates [**1**, X = R$_2$O(O)P] and SnCl$_4$, based on NMR and elemental analysis of the complex.[11] A stereochemical model involving a bidentate coordination of *N*-sulfinyl dienophile **1a** or **1b** to the chiral Lewis acid with the sulfinyl oxygen and the carbonyl oxygen or one of the sulfonyl oxygens, respectively, might explain the excellent stereochemical outcome in the stoichiometric catalyst reactions.[7a] Similarly, a strong (O,O) chelate for the HDA adducts **3a** or **3b** and the chiral Lewis acid will also explain an inhibited catalyst turnover in the catalytic reactions. The use of TMSOTf as an additive in combination with **4c**-Cu(OTf)$_2$ (Figure 1) has previously been reported by Evans et al. in the catalytic enantioselective aldol additions of enol silanes to pyruvate esters.[12] Silyl crossover experiments identified TMSOTf as an additive to accelerate these reactions. TMSOTf is known to be an extremely powerful silylating agent.[13] The presence of oxygen atoms in the HDA adducts **3** leads to a working hypothesis involving cleavage of the M-(O,O) chelate (M = Cu or Zn) by addition of TMSOTf. An increased catalytic turnover of the test system (Scheme 1) is possible according to this hypothesis. Indeed, a significant improvement of the turnover, as well as the *de* and *ee*, was observed when TMSOTf (100 mol-%) was used as an additive with 10 mol-% of catalyst **4a**-Cu(OTf)$_2$ or **4a**-Zn(OTf)$_2$. The results are shown in Table 1. The best results were obtained for **1a** with **4a**-Cu(OTf)$_2$ (10 mol-%) giving a 68% yield of *endo*-**3a** (98% *ee*, >90% *de*; Table 1, Entry 4), and for **1b** with **4a**-Zn(OTf)$_2$ (10 mol-%), giving an 86% yield of *endo*-**3b** (97% *ee*, >90% *de*; Table 1, Entry 14). The *de*'s (*endo*/*exo* ratios) of the products were determined by ^{1}H

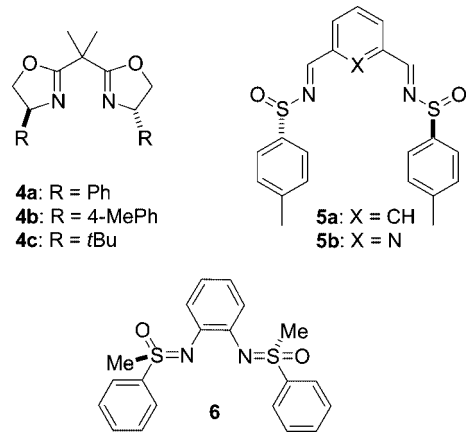


Figure 1. Chiral ligands tested.

Table 1. The effect of achiral additives (100 mol-%) on the HDA reactions of **1a** or **1b** with 1,3-cyclohexadiene with 10 mol-% of **4a**-Cu(OTf)$_2$ or **4a**-Zn(OTf)$_2$.

Entry	*N*-Sulfine	Additive	Chiral Lewis acid	*T* [°C]	Time [h]	Yield (%)[a]	Config. of *endo*-**3**	*endo*/*exo*[b]	% *ee*[c]
1	**1a**	–	*ent*-**4a**-Cu(OTf)$_2$	–55	22	25	(1*R*,2*S*,4*S*)	38:62	15
2	**1b**	–	*ent*-**4a**-Cu(OTf)$_2$	–85	24	93	(1*R*,2*S*,4*S*)	82:18	36
3	**1a**	TMSOTf	**4a**-Cu(OTf)$_2$	–75	22	85	(1*S*,2*R*,4*R*)	>95:<5	89
4	**1a**	TMSOTf	**4a**-Cu(OTf)$_2$	–75	4	68	(1*S*,2*R*,4*R*)	>95:<5	98
5	**1a**	TMSOTf	**4a**-Cu(OTf)$_2$	–75	1	54	(1*S*,2*R*,4*R*)	90:10	94
6	**1b**	TMSOTf	**4a**-Cu(OTf)$_2$	–75	22	56	(1*S*,2*R*,4*R*)	92:8	80
7	**1b**	TMSOTf	**4a**-Cu(OTf)$_2$	–75	4	60	(1*S*,2*R*,4*R*)	90:10	75
8	**1a**	TIPSOTf	**4a**-Cu(OTf)$_2$	–75	4	86	(1*S*,2*R*,4*R*)	>95:<5	88
9	**1b**	TIPSOTf	**4a**-Cu(OTf)$_2$	–75	4	74	(1*S*,2*R*,4*R*)	92:8	80
10	**1a**	DME	**4a**-Cu(OTf)$_2$	–75	4	15	–	55:45	–
11	**1a**	–	*ent*-**4a**-Zn(OTf)$_2$	–75	22	30	(1*R*,2*S*,4*S*)	75:25	61
12	**1b**	–	*ent*-**4a**-Zn(OTf)$_2$	–75	22	39	(1*R*,2*S*,4*S*)	92:8	78
13	**1a**	TMSOTf	**4a**-Zn(OTf)$_2$	–75	22	70	(1*S*,2*R*,4*R*)	92:8	86
14	**1b**	TMSOTf	**4a**-Zn(OTf)$_2$	–75	22	86	(1*S*,2*R*,4*R*)	>95:<5	97
15	**1b**	TMSOTf	**4a**-Zn(OTf)$_2$	–75	4	83	(1*S*,2*R*,4*R*)	>95:<5	96
16	**1b**	TMSOTf	**4a**-Zn(OTf)$_2$	–75	1	82	(1*S*,2*R*,4*R*)	>95:<5	94
17	**1a**	TIPSOTf	**4a**-Zn(OTf)$_2$	–75	4	62	(1*S*,2*R*,4*R*)	>95:<5	90
18	**1b**	TIPSOTf	**4a**-Zn(OTf)$_2$	–75	4	66	(1*S*,2*R*,4*R*)	83:17	82
19	**1b**	DME	**4a**-Zn(OTf)$_2$	–75	4	25	(1*S*,2*R*,4*R*)	84:16	47

[a] Isolated yield. [b] Determined by ^{1}H NMR (400 MHz) of the crude product. [c] Determined by chiral HPLC.

NMR (400 MHz) of the crude products, and a *de* >90% means that only one product was observed. The *ee* in the reaction of **1a** and **2**, catalyzed by **4a**-$Cu(OTf)_2$, was dependent on the reaction time. It appears from the results in Table 1 that the optimum reaction time is 4 h (98% *ee*, Table 1, Entry 4) and that longer reaction times erode the *ee* of *endo*-**3a** (22 h, 89% *ee*, Table 1, Entry 3). For **1b**, catalyzed by **4a**-$Zn(OTf)_2$, the *ee* was unaffected by a long reaction time (22 h, 97% *ee*, Table 1, Entry 14). Therefore, a reaction time of 4 h was chosen for both test reactions. Evaluation of triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and 1,2-dimethoxyethane (DME) as additives in the HDA test reactions revealed that TIPSOTf has an effect (for **1a**: 88% *ee*, Table 1, Entry 8; for **1b**: 82% *ee*, Table 1, Entry 18) but generally gives less enantioselectivity compared to TMSOTf. DME, expected to coordinate competitively with the Lewis acid and to help the release of the catalyst from the HDA adduct, improved neither the catalyst turnover nor the *ee* of the HDA products (**1a**: Table 1, Entry 10; **1b**: Table 1, Entry 19).

The relationship between the TMSOTf loading and the *ee* of the HDA products *endo*-**3a** and *endo*-**3b** was investigated for the test reactions (Scheme 1) catalyzed by 10 mol-% of **4a**-$Zn(OTf)_2$, as shown in Figure 2. For both reactions, the optimum additive loading was 100 mol-%. Since TMSOTf is a Lewis acid,[14] and loadings over 100 mol-% eroded the *ee* of the products, a non-stereoselective, catalyzed, background reaction may explain the lowered enantioslectivities.

Several solvents were screened with respect to stereochemical outcome of the HDA test reactions (Scheme 1 and Table 2). Solutions of the catalysts **4a**-$Cu(OTf)_2$ and **4a**-$Zn(OTf)_2$ in CH_2Cl_2, toluene, THF, and a 1:1 mixture of CH_2Cl_2 and toluene were generated by the standard procedure. The solvent survey (Table 2) revealed that CH_2Cl_2 was the optimal solvent with respect to yields and stereoselectivity (**1a**: 85% yield, 89% *ee*, Table 2, Entry 1; **1b**: 86% yield, 97% *ee*, Table 2, Entry 5). Toluene gave moderate *ee* (**1a**: 80% *ee*, Table 2, Entry 2; **1b**: 56% *ee*, Table 2, Entry 6), but the chiral Lewis acids were only slightly soluble in this system, which was reflected in low product yields (28% and 31%). However, when toluene was mixed with CH_2Cl_2, the yield doubled (Table 2, Entries 3 and 7). THF was not a suitable solvent. In fact, storing the *N*-sulfines in THF in the freezer decomposed these dienophiles.

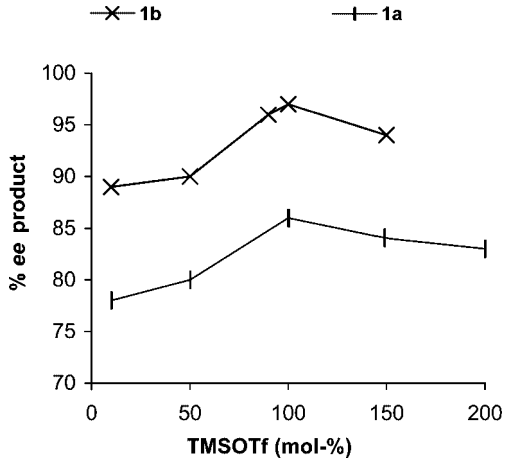


Figure 2. The effect of TMSOTf loading on the *ee* value (%) of the reaction of **1a** or **1b** with **2** in the presence of 10 mol-% of **4a**-$Zn(OTf)_2$.

The effect of catalyst loading on the yield and % *ee* of the HDA reactions of **1a** or **1b** and **2** with TMSOTf (100 mol-%) in CH_2Cl_2 at –75 °C (4 h) were tested. The relationship between catalyst loading and *ee* is shown in Figure 3. Unfortunately, an attempt to decrease the loading of **4a**-$Zn(OTf)_2$ to 5 mol-% (73% yield and 83% *ee*) and 2 mol-% (69% yield and 63% *ee*) reduced both the yield and *ee* of *endo*-**3b**. This was also the case with the **4a**-$Cu(OTf)_2$-catalyzed reaction of **1a** and **2** when catalyst loadings of 10 mol-% (85% yield and 96% *ee*), 5 mol-% (72% yield and 91% *ee*), 2 mol-% (62% yield and 89% *ee*), and 1 mol-% (44% yield and 85% *ee*) were tested. From this analysis, a catalyst loading of 10 mol-% for both catalysts was used in further studies.

The relationship between the enantiomeric purity of the chiral ligand **4a** and the *ee* of the product was investigated for the HDA test reactions shown in Scheme 1. In this study, 10 mol-% of the catalyst and 100 mol-% of TMSOTf were used. The results are plotted in Figure 4. A positive nonlinear effect (NLE)[15] was observed for the **4a**-$Zn(OTf)_2$-catalyzed reaction of **1b** and **2**. The deviation from linearity indicates that the active catalyst is a dimer or higher-order aggregate, and the homochiral species giving enantiomeric enrichment was more active than the heterochiral species giving racemic products. For the **4a**-$Cu(OTf)_2$-catalyzed reaction of **1a** and **2**, a linear relationship

Table 2. The effect of solvents on the HDA reactions of **1a** or **1b** and 1,3-cyclohexadiene (**2**) with 10 mol-% of **4a**-$Cu(OTf)_2$ or **4a**-$Zn(OTf)_2$ and 100 mol-% of TMSOTf at –75 °C for 22 h.

Entry	*N*-Sulfine	Solvent	Chiral Lewis acid	Yield (%)[a]	*endo*/*exo*[b]	% *ee*[c]
1	**1a**	CH_2Cl_2	**4a**-$Cu(OTf)_2$	85	>95:<5	89
2	**1a**	toluene	**4a**-$Cu(OTf)_2$	28	>95:<5	80
3	**1a**	toluene/CH_2Cl_2, 1:1	**4a**-$Cu(OTf)_2$	61	>95:<5	86
4	**1a**	THF	**4a**-$Cu(OTf)_2$	10	89:11	–
5	**1b**	CH_2Cl_2	**4a**-$Zn(OTf)_2$	86	>95:<5	97
6	**1b**	toluene	**4a**-$Zn(OTf)_2$	31	90:10	56
7	**1b**	toluene/CH_2Cl_2, 1:1	**4a**-$Zn(OTf)_2$	60	>95:<5	92
8	**1b**	THF	**4a**-$Zn(OTf)_2$	15	55:45	–

[a] Isolated yield. [b] Determined by ^1H NMR (400 MHz) of the crude product. [c] Determined by chiral HPLC.

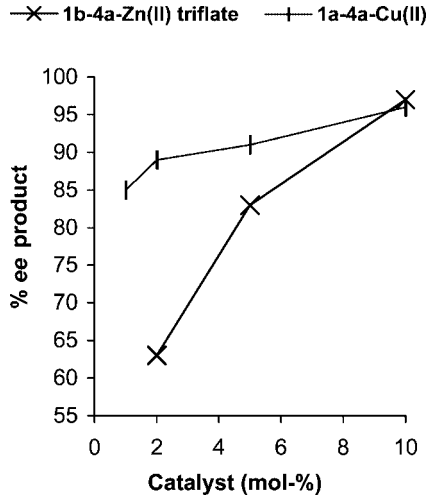


Figure 3. The effect of **4a**-Cu(OTf)$_2$ or **4a**-Zn(OTf)$_2$ loading on the % *ee* of the HDA reactions of **1a** or **1b**, respectively, and 1,3-cyclohexadiene (**2**) with TMSOTf (100 mol-%) as an achiral additive.

or a slightly positive NLE was observed. The result is in accordance with the linear relationship found by Evans et al. for **4a**-Cu(SbF$_6$)$_2$-catalysed HDA and ene reactions.[16] However, the result obtained herein deviates from our findings for the same reaction with a stoichiometric amount of catalyst, where a positive NLE was observed.[7a]

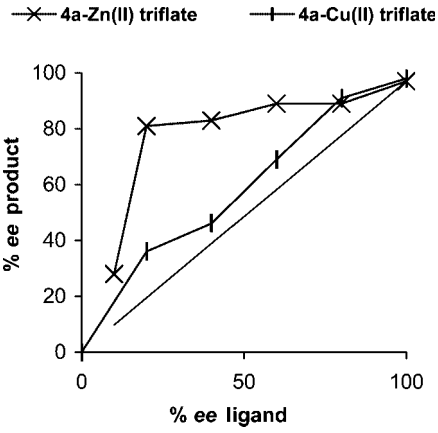
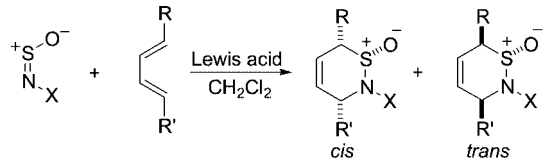


Figure 4. Investigation of nonlinear effects for the HDA reactions of **1a** or **1b** and **2**, catalyzed by **4a**-Cu(OTf)$_2$ (10 mol-%), or **4a**-Zn(OTf)$_2$ (10 mol-%), respectively, in the presence of TMSOTf (100 mol-%).

Dienes

The results of the **4a**-Cu(OTf)$_2$-catalyzed reaction of *N*-sulfine **1a** or **1b** with the acyclic dienes **7**–**10** (see Scheme 2) are presented in Table 3. Under the influence of the Lewis acids, reactions with the dienes **7**–**10** provided the *cis* isomers as the major products. For the unsymmetrical dienes **8** and **9**,[17] only the 3-substituted regioisomers **12** and **13**, respectively, were formed. Similar results have been published for the uncatalyzed HDA reactions of *N*-sulfines **1** (X = Ts, COTol) with 1-substituted dienes (R′ = Me, Ph, *p*-NO$_2$Ph, *p*-MeOPh), which usually provided the kinetically favored 3-substituted 1,2-thiazine 1-oxides at low temperature (5 °C) and the less crowded, thermodynamically favored, 6-substituted products at higher temperature (80 °C).[2e,18]



1a: X = Cbz
1b: X = Ts

7: R = R′ = Me
8: R = H, R′ = Me
9: R = H, R′ = Ph
10: R = Me, R′ = Ph

11a: R = R′ = Me, X = Cbz
11b: R = R′ = Me, X = Ts
12a: R = H, R′ = Me, X = Cbz
12b: R = H, R′ = Me, X = Ts
13a: R = H, R′ = Ph, X = Cbz
13b: R = H, R′ = Ph, X = Ts
14a: R = Me, R′ = Ph, X = Cbz
15a: R = Ph, R′ = Me, X = Cbz
14b: R = Me, R′ = Ph, X = Ts
15b: R = Ph, R′ = Me, X = Ts

Scheme 2. HDA reactions of **1a** or **1b** with acyclic dienes **7**–**10**.

The uncatalyzed HDA reaction of **10**[17,19] with *N*-sulfine **1a** or **1b** at room temperature for 22 h afforded mixtures of stereoisomers and regioisomers. For **1a**, a mixture of *cis*-**14a**, *trans*-**14a**, *cis*-**15a**, and *trans*-**15a** was formed in a ratio of 1:3.1:1:7.1 and in 86% total yield. For **1b**, a mixture of *cis*-**14b**, *cis*-**15b**, and *trans*-**15b** was formed in a ratio of 3.3:1.7:1 and in 90% total yield. The effect of adding stoichiometric amounts of **4a**-Cu(OTf)$_2$ to these reactions was amazing. For both **1a** and **1b**, only *cis*-**14a** (31% yield and 42% *ee*, Table 3, Entry 17) and *cis*-**14b** (50% yield and 71% *ee*, Table 3, Entry 19), respectively, were observed by ^{1}H NMR of the crude products.

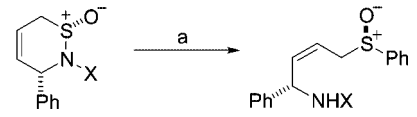
In general, stoichiometric amounts of **4a**-Cu(OTf)$_2$ provided cycloadducts **11**–**14** in better stereoselectivities (40–97% *ee* and 66% to >90% *de*) and yields (29–68%) than the **4a**-Zn(OTf)$_2$-promoted reactions (26–58% *ee*, 74% to >90% *de*, and 19–40% yield). Furthermore, higher *ee*'s were observed for *N*-sulfine **1b** with dienes **7** (97% *ee*, Table 3, Entry 4), **8** (87% *ee*, Table 3, Entry 9), **9** (92% *ee*, Table 3, Entry 15), and **10** (71% *ee*, Table 3, Entry 19) than for the reaction of **1a** (**7**: 70% *ee*, **8**: 77% *ee*, **9**: 40% *ee*, **10**: 42% *ee*, Table 3, Entries 1, 6, 12, and 17, respectively). The direction of the stereoselectivity was the same in all reactions where the absolute configuration was determined and the catalysts were working. The *ee* was, in general, determined by chiral HPLC analysis (with either a Chiralpak AD or Chiracel OD-H column) of the initial cycloadducts. For the HDA products *cis*-**13a** and *cis*-**13b**, a ring opening to **16a** and **16b**, respectively, with phenylmagnesium bromide was necessary in order to determine the % *ee* by chiral HPLC analysis (Scheme 3).

Attempts to perform the HDA reaction of **1a** and **8** with catalytic amounts (10 mol-%) of either **4a**-Cu(OTf)$_2$ or **4a**-Zn(OTf) at –45 °C for 22 h, without additive, afforded racemic *trans*-**12a** (>90% *de*) in ≈ 20% yield (Scheme 2). The effect of adding TMSOTf (100 mol-%) to the **4a**-Cu(OTf)$_2$-catalyzed reaction was remarkable. A switch in diastereo-

Table 3. Selected catalyzed HDA reactions of **1a** or **1b** with acyclic dienes **7**–**10**.

Entry	*N*-Sulfine	Lewis acid (mol-%)	*T* [°C]	time [h]	HDA adduct	Yield (%)[a]	Config. of *cis* isomer	*cis*/*trans*[b]	% *ee*[c]
1	**1a**	**4a**-Cu(OTf)$_2$ (100)	–45	22	**11a**	72	(1*R*,3*S*,6*R*)	>95:<5	70
2	**1a**	**4a**-Cu(OTf)$_2$ (10)[d]	–45	4	**11a**	39	(1*R*,3*S*,6*R*)	>95:<5	60
3	**1a**	**4b**-Cu(OTf)$_2$ (10)[d]	–45	4	**11a**	42	(1*R*,3*S*,6*R*)	>95:<5	66
4	**1b**	*ent*-**4a**-Cu(OTf)$_2$ (100)	–85	25	**11b**	68	(1*S*,3*R*,6*S*)	>95:<5	97
5	**1b**	**4a**-Cu(OTf)$_2$ (10)[d]	–75	4	**11b**	67	–	>95:<5	0
6	**1a**	*ent*-**4a**-Cu(OTf)$_2$ (100)	–45	22	**12a**	60	(1*S*,3*R*)	>95:<5	77
7	**1a**	**4a**-Cu(OTf)$_2$ (10)[d]	–45	4	**12a**	47	(1*R*,3*S*)	>95:<5	81
8	**1a**	**4b**-Cu(OTf)$_2$ (10)[d]	–45	4	**12a**	43	(1*R*,3*S*)	>95:<5	74
9	**1b**	*ent*-**4a**-Cu(OTf)$_2$ (100)	–85	22	**12b**	68	(1*S*,3*R*)	73:27	87
10	**1b**	**4a**-Cu(OTf)$_2$ (10)[d]	–75	2	**12b**	15	(1*S*,3*R*)	>95:<5	3
11	**1b**	**4a**-Zn(OTf)$_2$ (10)[d]	–75	4	**12b**	69	(1*S*,3*R*)	75:25	8
12	**1a**	**4a**-Cu(OTf) (100)	–40	22	**13a**	43	[e]	83:17	40
13	**1a**	**4a**-Cu(OTf)$_2$ (10)[d]	–40	4	**13a**	84	[e]	77:23	43
14	**1a**	**6**-Cu(OTf)$_2$ (10)[d]	–40	6	**13a**	38	[e]	94:6	18
15	**1b**	**4a**-Cu(OTf)$_2$ (100)	–45	22	**13b**	68	(1*R*,3*R*)	>95:<5	92
16	**1b**	**4a**-Cu(OTf)$_2$ (10)[d]	–45	4	–	0	–	–	–
17	**1a**	**4a**-Cu(OTf)$_2$ (100)	–40	22	**14a**	31	[e]	>95:<5[f]	42
18	**1a**	**4a**-Cu(OTf)$_2$ (10)[d]	–45	4	**14a**	46	[e]	>95:<5[f]	30
19	**1b**	**4a**-Cu(OTf)$_2$ (100)	–45	22	**14b**	50	[e]	>95:<5[f]	71
20	**1b**	**4a**-Cu(OTf)$_2$ (10)[d]	–45	4	–	0	–	–	–

[a] Isolated yield. [b] Determined by ^{1}H NMR (400 MHz) of the crude product. [c] Determined by chiral HPLC. [d] Reaction with 100 mol-% of TMSOTf. [e] The absolute configuration was not determined. [f] Only the *cis*-**14** HDA product was observed by ^{1}H NMR (400 MHz) of the crude product.



cis-**13a**: X = Cbz
cis-**13b**: X = Ts

16a: X = Cbz
16b: X = Ts

Scheme 3. Ring opening of *cis*-**13** to **16**, in order to determine the % *ee* by chiral HPLC analysis. a) PhMgBr, –60 °C, THF, **16a** (65% yield), **16b** (85% yield).

selectivity to *cis*-**12a** (>90% *de*) in 81% *ee* and 47% yield (Table 3, Entry 7) in a shorter reaction time (4 h) showed that the catalyst was working. Similarly, reactions with the dienes **7**, **9**, and **10** afforded the *cis* adducts in 39–84% yield, 54% to >90% *de*, and 30–60% *ee* (Table 3, Entries 2, 13, and 18, respectively). These results are comparable to those of the reactions promoted by stoichiometric amounts of **4a**-Cu(OTf)$_2$ (Table 3, Entries 1, 12, and 17). On the other hand, adding TMSOTf to similar experiments with **1b** gave rather disappointing results. Either full racemization or no cycloaddition at all was observed (Table 3, Entries 5, 10, 16, and 20). A competitive, uncatalyzed, HDA reaction may account for the racemic products.

Since TMSOTf is a Lewis acid,[14] test reactions were run with TMSOTf (100 mol-%) as the only promoter. Neither **7** nor **8** provided cycloadducts with **1a** at –45 °C in 4 h of reaction time.

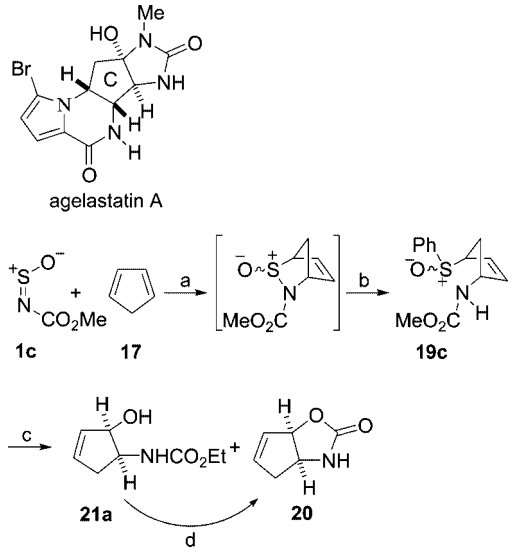
The moderate enantioselectivities observed for the reaction of acyclic dienes and **1a**, catalyzed by **4a**-Cu(OTf)$_2$, prompted us to screen other chiral ligands (shown in Figure 1). The most promising results are shown in Table 3. However, except for the new bis(oxazoline) analogue **4b**[20] (Table 3, Entries 3 and 8), none of the ligands compared favorably with **4a** in either stereoselectivity or yield. Bolm and Simić's new and promising C_2-symmetric bis(sulfoximine) **6** did not improve the *ee*'s in the tested reactions (e.g. Table 3, Entry 14).[21] In Cu(OTf)$_2$-catalyzed reactions with ligands **5a**[22] and **5b**,[23] no products were obtained in either case.

Not surprisingly, attempts to react either sulfinyl compound **1a** or **1b** with (*Z*,*Z*)-1,3-cyclooctadiene under uncatalyzed conditions or in the presence of **4a**-M(OTf)$_2$ (M = Cu or Zn) gave no HDA products at all. Little or no reactivity of (*Z*,*Z*)-1,3-cyclooctadiene in HDA reactions with other hetero dienophiles has also been observed by others.[24]

The general rate enhancement observed in the reactions of **1a** with catalytic amounts of **4a**-Cu(OTf)$_2$ (10 mol-%) in combination with 100 mol-% of TMSOTf (4 h reaction time) as compared to reactions with stoichiometric amounts of **4a**-Cu(OTf)$_2$ (22 h reaction time), indicates that the role of TMSOTf is more complicated than first expected. In addition to the assumed assistance of the release of the chiral catalyst from the HDA adducts, TMSOTf may also dissolve or break down aggregates composed of the catalyst, *N*-sulfine, and dienophile. Support for the latter comes from the nearly linear relationship observed between the enantiomeric purity of the chiral ligand **4a** and the *ee* of the product for the HDA test reactions (see Scheme 1 and Figure 3) containing 10 mol-% of **4a**-Cu(OTf)$_2$ and 100 mol-% of TMSOTf, versus the positive nonlinear effect found in the stoichiometric reaction.[7a] Furthermore, HDA reactions of **1a** and **8**, loaded with 100 mol-% of both **4a**-Cu(OTf)$_2$ and TMSOTf, showed that the reaction was complete in less than 1 h (*cis*-**12a**, 40% yield, >90% *de*, and 83% *ee*). Prolonged reaction times up to 22 h neither increased the yield nor changed the stereoselectivity.

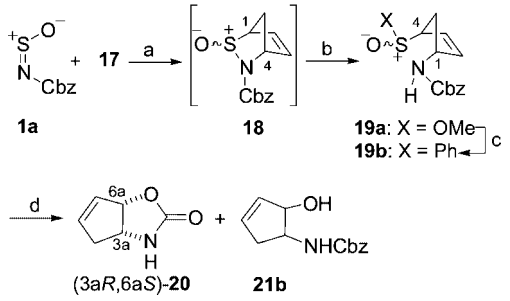
Application

Recently, Weinreb and co-workers reported the first racemic total synthesis of the antitumor marine sponge alkaloid agelastatin A (Scheme 4).[8] The synthesis started with an uncatalyzed HDA reaction between cyclopentadiene (**17**) and *N*-sulfinyl methyl carbamate (**1c**) at 0 °C in benzene to afford the HDA adduct in high yield (Scheme 4). Since this compound was prone to a retro Diels–Alder reaction at room temperature, it was immediately treated with phenylmagnesium bromide to produce the allylic sulfoxide **19c** in 86% overall yield. The latter compound was further rearranged to the olefinic oxazolidinone **20**, which, in turn, controls the construction of the relative configuration of the chiral part in agelastatin A (C-ring).



Scheme 4. Weinreb's racemic synthesis of the olefinic oxazolidinone **20**, a precursor of the C-ring in agelastatin A.[8] a) PhH, 0 °C; b) PhMgBr, THF, –60 °C, 86% (two steps); c) HMPT, EtOH, 80 °C, **20** (44%), **21a** (40%); d) KO*t*Bu, THF, 83%.

Herein, an asymmetric route to oxazolidinone **20**, following Weinreb's protocol,[8] is presented (Scheme 5). The asymmetric HDA reaction between **1a** and cyclopentadiene (**17**), catalyzed by 10 mol-% of **4a**-Cu(OTf)$_2$ in CH_2Cl_2 at –75 °C for 3 h, was quenched by the addition of methanol to produce the allylic sulfoxide **19a** (X = OMe). A change of ring-opening reagents from the original Weinreb protocol[8] was necessary due to the incompatibility of CH_2Cl_2 and phenylmagnesium bromide. Attempts to rearrange **19a** to **20** with hexamethylphosphorous triamide (HMPT) in refluxing ethanol did not work and, therefore, **19a** (X = OMe) was further transformed into **19b** (X = Ph). This three-step procedure, (a–c in one pot) starting from **1a** and **17**, afforded an inseparable 4:1 mixture of two sulfoxide epimers of **19b** in 50% yield. The enantiomeric purity of the major and minor epimers was determined to be 80% and 16% *ee*, respectively, by chiral HPLC analysis.



Scheme 5. An enantioselective route to oxazolidinone **20**: a) **4a**-Cu(OTf)$_2$ (10 mol-%), TMSOTf (100 mol-%), CH_2Cl_2, –75 °C, 3 h; b) MeOH, –75 °C → room temp., 4 h; c) PhMgBr (2 equiv.), THF, –60 °C, a)–c) one pot 50% yield; d) HMPT, EtOH, 80 °C, (3a*R*,6a*S*)-**20** (64%), **21b** (19%).

Upon heating with HMPT in ethanol, the sulfoxide mixture **19b** underwent a [2,3]-sigmatropic rearrangement to afford the olefinic oxazolidinone (3a*R*,6a*S*)-**20**[25] in 64% yield and the uncyclized hydroxy benzyl carbamate **21b** in 19% yield. According to Weinreb and co-workers, the ethyl carbamate relative of the latter compound (**21a**, Scheme 4) can be cyclized to **20** with potassium *tert*-butoxide in high yield.[8]

Stereochemical Model

We have earlier pointed out that a tetrahedral metal center or a stereochemically equivalent geometry may explain the stereochemical outcome of the HDA reactions of *N*-sulfinyl dieneophiles **1a** and **1b** catalyzed by either **4a**-Zn(OTf)$_2$ or **4a**-Cu(OTf)$_2$ when the catalysts were working.[7a,7b] All thiazine oxides had the *R* configuration at sulfur (see below for the determination of the absolute configuration of the HDA adducts), implying that all dienes approach dienophiles **1a** and **1b** from the same side. The postulated model shown in Figure 5 assumes that *N*-sulfinyl dienophiles **1a** and **1b** (last compound is not shown) have a bidentate coordination to the chiral Lewis acid with the sulfinyl oxygen and the carbonyl oxygen (for **1a**) or one of the sulfonyl oxygens (for **1b**). While the possibility of tetrahedral geometry for Cu^{II} complexes has been the subject of some debate,[16,26] tetrahedral metal centers are well known for Zn^{II} complexes.[27]

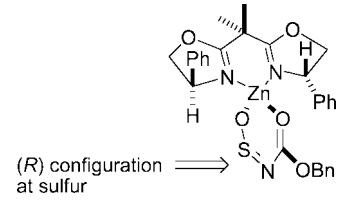


Figure 5. Postulated intermediate with a tetrahedral arrangement.

Configuration of the Diels–Alder Products

The determination of the absolute configuration of the HDA adducts *endo*-**3**[7c–7d] and *cis*-**11**–*cis*-**12**[7a] have been

described elsewhere. For the thiazine oxides *trans*-**13a**, *trans*-**13b**, *trans*-**14a**, *cis*-**14b**, *cis*/*trans*-**15a**, and *cis*-**15b**, the relative configurations were determined by X-ray analyses.[28] For *cis*-**13b**, X-ray analysis revealed the absolute configuration.[28] The absolute configuration of the unstable thiazine oxide **18** was established by chemical correlation with the known cyclic carbamate (3a*R*,6a*S*)-**20**[25] (Scheme 5). The 4:1 mixture of sulfur epimers **19b** was rearranged and cyclized to (3a*R*,6a*S*)-**20**,[25] and thus, the major thiazine oxide **18** was found to have a (1*S*,4*R*) configuration. A major *endo*-**18** product with a (1*S*,2*R*,4*R*) configuration fits with the stereochemical model described above.

Conclusions

In conclusion, catalytic asymmetric HDA reactions of *N*-sulfinyl dienophiles with bis(oxazoline)copper(II) and -zinc(II) triflates have been presented. The presence of the additive TMSOTf was crucial to achieving catalytic turnover. The copper catalyst was found to be more efficient. Two *N*-sulfinyl dienophiles, **1a** and **1b**, were tested throughout this study. In general, the Cbz-substituted sulfine **1a** was more suitable under catalytic conditions than the Ts-substituted sulfine **1b**. For **1b**, a pronounced, competitive, uncatalyzed, HDA reaction reduced the impact of the catalyst. The present study included both cyclic and acyclic dienes. For the cyclic dienes, good yields and up to 98% *ee* was obtained. The acyclic dienes, however, were less successful under the catalytic conditions. The configurations of several cycloadducts have been determined and can be explained by a stereochemical model proposing a tetrahedral metal center. The synthetic potential of the reaction has been demonstrated in the enantioselective synthesis of (3a*R*,6a*S*)-3,3a,4,6a-tetrahydrocyclopenta[*d*][1,3]oxazol-2-one, a precursor of the C-ring in agelastatin A.

Experimental Section

General: Benzyl *N*-sulfinylcarbamate (**1a**)[9] and *N*-sulfinyl-4-toluenesulfonamide (**1b**)[2b] were prepared according to the literature procedure and stored in the freezer as solutions in dry CH_2Cl_2. (*S*,*S*)-2,2′-Isopropylidenebis(4-phenyl-2-oxazoline) (**4a**),[10] [*S*(*S*),*S*′(*S*)]-*N*,*N*′-(2,6-pyridinediyldimethylidyne)bis[*p*-toluenesulfinamide] (**5b**),[23] (*S*,*S*)-1,2-bis(*S*-methyl-*S*-phenylsulfonimidoyl)-benzene (**6**),[21] (*E*)-1-phenyl-1,3-butadiene (**9**),[17] and (1*E*,3*E*)-1-methyl-4-phenylbutadiene (**10**),[17,19] were prepared according to the literature procedure. Analytical data for *endo*-**3**, *exo*-**3**,[7d] *cis*-**11**, *trans*-**11**, *cis*-**12**, and *trans*-**12**[7a] are described elsewhere. Solvents were dried according to standard procedures.[29] TLC was performed on silica gel plates and visualized with UV light and a phosphomolybdic acid in ethanol solution. Reaction products were purified by flash chromatography (FC) with silica gel (35–70 μm). ^{1}H NMR (300 MHz, 400 MHz, and 600 MHz) and ^{13}C NMR (75 MHz, 100 MHz, and 150 MHz) spectra were obtained from solutions of $CDCl_3$, and chemical shifts were assigned by 2D correlation techniques. The electron-impact mass spectra (EIMS) were recorded at 70 eV with a direct inlet and the chemical ionozation mass spectra (CIMS) were obtained with methane (ionized at 200 eV) as the carrier gas. The high resolution mass spectra (HREIMS and HRCIMS) were obtained with perfluorokerozene (PFK) as a standard to provide the reference masses. The elemental analyses were performed at the Institute of Chemical Technology, Prague Central Laboratories, Czech Republic. HPLC was performed with a 4.6 mm × 25 cm Daicel Chiralpak AD, Chiralcel OD-H, or Chiralcel OJ column. Melting points are reported uncorrected.

General Procedure for the Uncatalyzed HDA Reaction: To a solution of the *N*-sulfinyl compound **1** (X = Cbz, 0.6 M, X = Ts, 0.5 M, 1.8 mmol) in dry CH_2Cl_2 was added a solution of the diene (1 M, 1.5–2.5 equiv.) in dry CH_2Cl_2. The reaction was stirred at room temperature for 24 h under a N_2 atmosphere. The solvent was evaporated in vacuo, and the crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and, on some occasions, also the regioisomeric ratio. The crude product was purified by FC.

General Catalyst Preparation. Preparation of the Bis(oxazoline)copper(II) Catalyst [4a-Cu(OTf)$_2$] or the Bis(oxazoline)zinc(II) Catalyst [4a-Zn(OTf)$_2$]:[10] An oven-dried round-bottomed flask was charged with copper(II) triflate or zinc(II) triflate (0.025 mmol) under an argon atmosphere. To this mixture, dry CH_2Cl_2 (2 mL) and a solution of the phenyl bis(oxazoline) ligand (**4a**, 0.5 M, 52 μL, 0.026 mmol) in CH_2Cl_2 were added, and the resulting suspension was stirred for 2 h, at which time, most of the solids had dissolved. A light green solution was observed in the generation of the copper(II) catalyst, while no color was observed in the preparation of the zinc catalyst.

General Procedure for the Asymmetric HDA Reaction: A solution of the *N*-sulfinyl compound **1** (620 μL, 0.4 M, 0.248 mmol) in CH_2Cl_2 was added to a precooled solution of the catalyst at –75 °C. A precooled solution of the diene (2 equiv.) in CH_2Cl_2 (500 μL) was added to the reaction mixture, followed by the addition of TMSOTf (1 equiv.). The diene solution was added slowly along the wall of the round-bottomed flask. The reaction mixture was stirred at –75 °C for 1–22 h and quenched by the addition of phosphate buffer (pH 7, 4 mL). The reaction was warmed to room temperature and was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. ^{1}H NMR of the crude product revealed the diastereomeric ratio. The crude was purified by FC, and the *ee* was determined by chiral HPLC.

HDA Reactions for the Investigation of the Nonlinear Effect (10 mol-% of Catalyst): Catalysts of different enantiomeric compositions were prepared according to the procedure described above. The scalemic mixtures of the bis(oxazoline) ligand were obtained by mixing **4a** (0.5 M in CH_2Cl_2) and *ent*-**4a** (*ent* = enantiomer, 0.5 M in CH_2Cl_2) under an argon atmosphere before addition to the reaction. The HDA reactions were performed at –75 °C for 4 h, as described in the general procedure given above.

Benzyl 3,6-Dihydro-3-phenyl-1λ^4,2-thiazine-2-carboxylate (13a): An asymmetric HDA reaction between **1a** and (*E*)-1-phenyl-1,3-butadiene (**9**),[17] catalyzed by **4a**-Cu(OTf)$_2$ (10 mol-%) according to the general procedure, afforded a mixture of *cis*-**13a** and *trans*-**13a** (3.4:1). FC (EtOAc/pentane, 50:50) of the crude product yielded 105.4 mg (65% yield) of *cis*-**13a** as a colorless, viscous oil, and 31.0 mg (19% yield) of *trans*-**13a** as a white solid. Analytical data for *cis*-**13a**: R_f (EtOAc/pentane, 50:50) = 0.28. $[\alpha]_D^{20}$ = +7.9 (*c* = 1, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.2 Hz, 2 H, Ph), 7.34–7.30 (m, 4 H, Ph), 7.28–7.25 (m, 4 H, Ph), 6.05 (dt, *J* = 10.2, 3 Hz, 1 H, 4-H), 5.82–5.79 (m, 1 H, 5-H), 5.46 (br. s, 1 H, 3-H), 5.08 (AB, *J* = 12.5 Hz, 2 H, Bn), 3.57 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H, 6-H), 3.46–3.42 (m, 1 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.2 (C=O), 140.2, 135.2, 130.3 (4-C),

129.3, 128.8, 128.7, 128.6, 128.4, 127.9, 112.4 (5-C), 68.9 (Bn), 58.6 (3-C), 48.7 (6-C) ppm. IR (KBr): $\tilde{\nu}$ = 3059 (w), 1708 (s, C=O), 1494 (m), 1452 (m), 1439 (m), 1380 (m), 1299 (s), 1199 (m), 1147 (m), 1093 (m) cm^{-1}. EIMS: *m*/*z* (%) = 328 (2), 327 (9) $[M]^+$, 279 (6), 235 (9), 131 (11), 130 (100), 129 (77), 128 (43), 115 (29), 107 (21), 91 (91). $C_{18}H_{17}NO_3S$ (327.09): calcd. C 66.03, H 5.23, N 4.28; found C 65.79, H 5.35, N 4.21. The optical purity of the product was determined to be 43% *ee* by transformation to **16a** (experimental details are shown below). Analytical data for *trans*-**13a**: R_f (EtOAc/pentane, 50:50) = 0.18. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 6 H, Ph); 7.22–7.15 (m, 4 H, Ph), 6.33 (ddd, *J* = 5.4, 4, 2 Hz, 1 H, 4-H), 5.81–5.78 (m, 1 H, 5-H); 5.53 (d, *J* = 5.4 Hz, 1 H, 3-H), 5.15 (AB, *J* = 9.6 Hz, 2 H, Bn), 3.61 (m, 2 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.9 (C=O), 140.3, 135.0, 132.5 (4-C), 129.1, 128.7, 128.6, 128.2, 127.8, 126.1, 112.5 (5-C), 69.3 (Bn), 57.5 (3-C), 48.1 (6-C) ppm. IR (KBr): $\tilde{\nu}$ = 3059 (w), 1708 (s, C=O), 1494 (m), 1452 (m), 1439 (m), 1380 (m), 1299 (s), 1199 (m), 1147 (m), 1093 (m) cm^{-1}. EIMS: *m*/*z* (%) = 327 (6) $[M]^+$, 279 (13), 235 (10), 130 (90), 129 (63), 128 (32), 127 (11), 115 (28), 107 (18), 91 (100). $C_{18}H_{17}NO_3S$ (327.09): calcd. C 66.03, H 5.23 N 4.28; found C 65.75, H 5.52, N 4.41. The relative configuration of *trans*-**13a** (1*R**,3*S**) was corroborated by X-ray crystallographic analysis.[28] A racemic sample melted at 132–133 °C (from CH_2Cl_2/pentane/EtOAc).

Ring Opening of *cis*-13a to 16a in Order to Determine the *ee* Value by Chiral HPLC: A solution of PhMgBr (1 M, 360 μL, 0.36 mmol) in THF was added to a stirred solution of *cis*-**13a** {$[\alpha]_D^{20}$ = +7.9 (*c* = 1, CH_2Cl_2), 119 mg, 0.36 mmol} in dry THF (5 mL) at –60 °C. The resultant mixture was stirred for 30 min and then hydrolyzed with saturated aqueous NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by FC (EtOAc/pentane, 33:67 to 50:50) yielded the allylic sulfoxide **16a** (95.4 mg, 65%) as a colorless oil. Analytical data for **16a**: $[\alpha]_D^{20}$ = –46.8 (*c* = 1.0, CH_2Cl_2). HPLC (Chiralpak AD, *i*PrOH/hexane, 20:80, 1 mL min^{-1}, 230 nm): 43% *ee*, t_R 15.1 min (major) and 27.0 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (br. s, 2 H, Ph), 7.49–7.40 (m, 3 H, Ph), 7.36–7.28 (m, 8 H, Ph), 7.22–7.17 (m, 2 H, Ph), 5.91 (app. t, *J* = 8.8 Hz, 1 H, 2-H), 5.67–5.54 (m, 1 H, 3-H), 5.42 (br. s, 2 H, 1-H/NH), 5.11 (s, 2 H, Bn), 3.88–3.73 (m, 1 H, 4-H), 3.72–3.65 (m, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (C=O), 143.2, 140.7, 137.4 (2-C), 136.5, 131.3, 129.4, 129.0, 128.8, 128.4, 128.3, 127.9, 126.7, 124.4, 119.8 (3-C), 76.8 (1-C), 67.2 (Bn), 55.1 (4-C) ppm. IR (neat): $\tilde{\nu}$ = 3285 (m), 3059 (w), 3030 (w), 2923 (w), 1716 (s), 1533 (m), 1252 (m), 1085 (m), 1036 (s) cm^{-1}. CIMS: *m*/*z* (%) = 406 (4) $[M + 1]^+$, 281 (11), 280 (35), 279 (37), 255 (17), 240 (10), 220 (13), 218 (16), 188 (18), 172 (17), 171 (14), 130 (12), 129 (34), 126 (11), 125 (19), 109 (11), 108 (23), 107 (13), 91 (100). $C_{24}H_{23}NO_3S$ (405.14): calcd. C 71.08, H 5.72, N 3.45 S 7.91; found C 70.88, H 5.71, N 3.45, S 7.62.

3,6-Dihydro-3-phenyl-2-tosyl-1λ⁴,2-thiazine 1-Oxide (13b): The asymmetric HDA reaction between *N*-sulfinyl **1b** and (*E*)-1-phenyl-1,3-butadiene (**9**),[17] catalyzed by **4a**-$Cu(OTf)_2$ (100 mol-%) according to the general procedure, afforded exclusively *cis*-**13b**. FC (EtOAc/pentane, 50:50) of the crude product yielded 86.2 mg (68% yield) of *cis*-**13b** as a white solid. Analytical data for *cis*-**13b** (1*R*,3*R*): R_f (EtOAc/pentane, 50:50) = 0.33. $[\alpha]_D^{20}$ = –49.6 (*c* = 1.0, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.28–7.26 (m, 2 H, Ph), 7.25 (app. d, *J* = 10.8 Hz, 2 H, Ts), 7.17–7.09 (m, 3 H, Ph), 6.98 (app. d, *J* = 10.8 Hz, 2 H, Ts), 5.99 (dt, *J* = 10.8, 2.8 Hz, 1 H, 4-H), 5.81–5.77 (m, 1 H, 5-H), 5.54 (dd, *J* = 12, 4.2 Hz, 1 H, 3-H), 3.65 (dd, *J* = 15.6, 7.2 Hz, 1 H, 6-H), 3.53–3.47 (m, 1 H, 6-H), 2.30 (s, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.0, 137.3, 136.8, 130.3 (4-C), 129.4, 129.38, 128.5, 127.9, 127.1, 112.1 (5-C), 59.8 (3-C), 49.8 (6-C), 21.3 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3056 (w), 1598 (m), 1494 (m), 1453 (m), 1355 (s), 1303 (m), 1183 (m), 1166 (s), 1101 (m), 1067 (m) cm^{-1}. EIMS: *m*/*z* (%) = 347 (0.1) $[M]^+$, 260 (7), 172 (5), 171 (50), 155 (45), 130 (14), 129 (14), 108 (13), 107 (16), 91 (100), 65 (20). $C_{17}H_{17}NO_3S_2$ (347.06): C 58.77, H 4.93, N 4.03; found C 58.99, H 5.21, N 3.73. The absolute configuration of *cis*-**13b** (1*R*,3*R*) was corroborated by X-ray crystallographic analysis.[28] The optical purity of the product was determined to be 92% *ee* by transformation to **16b** (experimental details are shown below). A racemic sample of *cis*-**13b** melted at 116–118 °C (from CH_2Cl_2/pentane/EtOAc). The uncatalyzed HDA reaction between **1b** and **9** afforded a mixture of *cis*-**13b** and *trans*-**13b** (3:1). FC (EtOAc/pentane, 50:50) of the crude product yielded 375.0 mg (60% yield) of *cis*-**13b** as a white solid and 125.0 mg (20% yield) of *trans*-**13b** as a white solid. Analytical data for *trans*-**13b** (1*R**,3*S**): R_f (EtOAc/pentane, 50:50) = 0.17. M.p. 121–123 °C (from CH_2Cl_2/pentane/EtOAc). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.37 (app. d, *J* = 9 Hz, 2 H, Ts), 7.22 (app. tt, *J* = 7.2, 2.4 Hz, 1 H, Ph), 7.18–7.15 (m, 2 H, Ph), 7.13 (app. d, *J* = 9 Hz, 2 H, Ts), 7.09–7.07 (m, 2 H, Ph), 6.04 (ddd, *J* = 7.2, 4.8, 3.0 Hz, 1 H, 4-H), 5.71–5.66 (m, 1 H, 5-H), 5.21–5.19 (m, 1 H, 3-H), 3.74 (app. dq, *J* = 16, 4.2 Hz, 1 H, 6-H), 3.62 (ddd, *J* = 15.9, 8.4, 1.8 Hz, 1 H, 6-H), 2.4 (s, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.5, 137.2, 135.9, 132.4 (4-C), 129.6, 128.7, 128.5, 128.4, 128.0, 111.2 (5-C), 58.7 (3-C), 50.2 (6-C), 21.8 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3060 (w), 1596 (m), 1492 (m), 1453 (s), 1339 (m), 1183 (m), 1113 (m), 1080 (m), 1062 (m), 974 (m), 928 (m) cm^{-1}. CIMS: *m*/*z* (%) = 348 (7) $[M + 1]^+$, 219 (11), 218 (86), 216 (16), 172 (13), 155 (100), 131 (34), 130 (71), 129 (47), 115 (21), 91 (48). $C_{17}H_{17}NO_3S_2$ (347.06): calcd. C 58.77, H 4.93, N 4.03; found C 58.68, H 4.92, N 4.17. The relative configuration of *trans*-**13b** (1*R**,3*S**) was corroborated by X-ray crystallographic analysis.[28]

Ring Opening of *cis*-13b to 16b in Order to Determine the *ee* Value by Chiral HPLC: *cis*-**13b** (1*R*,3*R*), $[\alpha]_D^{20}$ = –49.6 (*c* = 1.0, CH_2Cl_2), was ring opened by PhMgBr according to the procedure described above for the ring opening of *cis*-**13a**. This afforded **16b** (173.6 mg, 85% yield) as a white solid. Analytical data for **16b**: $[\alpha]_D^{20}$ = –222 (*c* = 1.0, CH_2Cl_2). HPLC (Chiralcel OJ, *i*PrOH/hexane, 30:70, 0.5 mL min^{-1}, 230 nm): 92% *ee*, t_R 27.9 min [1*S*,*S*(*R*) isomer] and 33.5 min [1*R*,*S*(*S*) isomer]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (app. d, *J* = 8.4 Hz, 2 H, Ts), 7.58–7.53 (m, 2 H, Ph), 7.52–7.45 (m, 3 H, Ph), 7.22–7.12 (m, 7 H, Ph/Ts), 6.00 (d, *J* = 5.2 Hz, 1 H, NH), 5.85 (dd, *J* = 10.8, 7.6 Hz, 1 H, 2-H), 5.22 (dq, *J* = 8.4, 1.2 Hz, 1 H, 3-H), 4.99 (t, *J* = 6 Hz, 1 H, 1-H), 3.78 (ddd, *J* = 8.4, 4.8, 1.2 Hz, 1 H, 4-H), 3.41 (dd, *J* = 8.0, 5.6 Hz, 1 H, 4-H), 2.38 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 142.0, 139.9, 138.7 (2-C), 137.8, 131.6, 129.5, 129.4, 128.8, 127.9, 127.5, 127.3, 124.4, 118.6 (3-C), 55.4 (1-C), 53.7 (4-C), 21.7 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3250 (m), 3060 (m), 2920 (w), 1598 (s), 1493 (s), 1443 (s), 1327 (s), 1161 (s) cm^{-1}. CIMS: *m*/*z* (%) = 426 (0.6) $[M + 1]^+$, 425 (2) $[M]^+$, 300 (20), 299 (100), 297 (27), 259 (61), 254 (19), 155 (49), 145 (17), 144 (86), 143 (32), 125 (28), 91 (53). $C_{23}H_{23}NO_3S_2$ (425.11): calcd. C 64.91, H 5.45, N 3.29; found C 64.84, H 5.39, N 3.01. A racemic sample of **16b** melted at 58–59 °C.

Benzyl 3,6-Dihydro-6-methyl-3-phenyl-1λ⁴,2-thiazine-2-carboxylate (14a) and Benzyl 3,6-Dihydro-3-methyl-6-phenyl-1λ⁴,2-thiazine-2-carboxylate (15a): The uncatalyzed reaction between **1a** and (1*E*,3*E*)-1-methyl-4-phenylbutadiene (**10**),[17,19] according to the general procedure, afforded a mixture of *cis*-**14a**, *trans*-**14a**, *cis*-**15a**, and *trans*-**15a** in a ratio of 1:3.1:1:7.1. FC (EtOAc/pentane, 33:67

to 50:50) of the crude product yielded 134 mg (22% yield) of *trans*-**14a**as a white solid, 309 mg (50% yield) of *trans*-**15a** as white solid, and a third fraction containing a mixture of *cis*-**14a** and *cis*-**15a**. FC (Et_2O/CH_2Cl_2, 5:95) of the latter fraction afforded 42.6 mg (7% yield) of *cis*-**14a** and 42.6 mg (7% yield) of *cis*-**15a**, both as white solids. Analytical data for *cis*-**14a** (1*R**,3*R**,6*R**): R_f (EtOAc/pentane, 50:50) = 0.35. M.p. 121–122 °C (from CH_2Cl_2/pentane). HPLC (Chiralpak AD, *i*PrOH/hexane, 40:60, 0.7 mL min^{-1}, 230 nm): t_R 9.5 min and 11.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.2 Hz, 2 H, Ph), 7.36–7.30 (m, 5 H, Ph), 7.25 (tt, *J* = 8.4, 1.2 Hz, 3 H, Ph), 5.97 (dt, *J* = 8, 2.8 Hz, 1 H, 4-H), 5.48 (dt, *J* = 9.6, 3.2 Hz, 1 H, 5-H), 5.40 (dd, *J* = 6.4, 3.2 Hz, 1 H, 3-H), 5.18 (AB, *J* = 12 Hz, 1 H, Bn), 5.08 (AB, *J* = 12 Hz, 1 H, Bn), 3.43–3.36 (m, 1 H, 6-H), 1.56 (d, *J* = 7.6 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.0 (C=O), 140.2, 135.2, 130.0 (4-C), 128.8, 128.7, 128.6, 128.4, 127.8, 119.6 (5-C), 68.9 (Bn), 58.5 (3-C), 52.3 (6-C), 16.1 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3032 (w), 1702 (s, C=O), 1493 (m), 1455 (s), 1385 (m), 1375 (m), 1287 (s), 1113 (m), 1077 (s) cm^{-1}. EIMS: *m*/*z* (%) = 341 (4) [M]$^+$, 144 (41), 129 (11), 91 (100), 84 (18). HRCIMS: calcd. for $C_{19}H_{19}NO_3S$ [M + 1]$^+$ 342.1164; found 342.1166. $C_{19}H_{19}NO_3S$ (341.11): calcd. C 66.84, H 5.61, N 4.10, S 9.39; found C 66.58, H 5.65, N 4.05, S 9.38. Analytical data for *trans*-**14a** (1*R**,3*S**,6*S**): R_f (EtOAc/pentane, 50:50) = 0.11. M.p. 110–111 °C (from CH_2Cl_2/pentane). HPLC (Chiralpak AD, *i*PrOH/hexane, 40:60, 0.7 mL min^{-1}, 230 nm): t_R 11.6 min and 13.7 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 8 H, Ph), 7.14–7.12 (m, 2 H, Ph), 5.95 (dd, *J* = 10.8, 3.6 Hz, 1 H, 4-H); 5.77 (ddd, *J* = 6.8, 4, 1.6 Hz, 1 H, 5-H), 5.35–5.34 (m, 1 H, 3-H), 5.15 (AB, *J* = 12 Hz, 1 H, Bn), 5.06 (AB, *J* = 12 Hz, 1 H, Bn), 3.56–3.49 (m, 1 H, 6-H), 1.56 (d, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.0 (C=O), 140.1, 135.0, 130.0 (4-C), 129.1, 128.7, 128.6, 128.2, 127.6, 126.6, 117.6 (5-C), 69.3 (Bn), 56.7 (3-C), 54.2 (6-C), 16.7 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3062 (w), 1732 (s, C=O), 1495 (m), 1449 (m), 1384 (m), 1281 (s), 1247 (s), 1097 (s), 1051 (s) cm^{-1}. EIMS: *m*/*z* (%) = 341 (1) [M]$^+$, 151 (6), 144 (55), 129 (100), 128 (52), 115 (20), 107 (37), 91 (95). HRCIMS: calcd. for $C_{19}H_{19}NO_3S$ [M + 1]$^+$ 342.1164; found 342.1164. $C_{19}H_{19}NO_3S$ (341.11): calcd. C 66.84, H 5.61, N 4.10, S 9.39; found C 66.82, H 5.52, N 4.13, S 9.60. The relative configuration of *trans*-**14a** (1*R**,3*S**,6*S**) was corroborated by X-ray crystallographic analysis.[28] Analytical data for *cis*-**15a** (1*R**,3*S**,6*S**): R_f (EtOAc/pentane, 50:50) = 0.48. M.p. 123–124 °C (from CH_2Cl_2/pentane). HPLC (Chiralpak AD, *i*PrOH/hexane, 40:60, 0.7 mL min^{-1}, 230 nm): t_R 7.0 min and 8.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 10 H, Ph), 6.14 (dt, *J* = 11.4, 3.0 Hz, 1 H, 4-H), 5.76 (dt, *J* = 11.1, 2.4 Hz, 1 H, 5-H), 5.31 (AB, *J* = 12.6 Hz, 1 H, Bn), 5.28 (AB, *J* = 12 Hz, 1 H, Bn), 4.64–4.60 (m, 1 H, 3-H), 4.52 (dd, *J* = 6, 3.0 Hz, 1 H, 6-H), 1.54 (d, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.8 (C=O), 135.4, 134.7, 131.8 (4-C), 129.9, 129.2, 129.1, 128.9, 128.7, 128.4, 118.1 (5-C), 68.8 (Bn), 63.8 (6-C), 49.8 (3-C), 22.4 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3032 (w), 1702 (s, C=O), 1493 (m), 1455 (s), 1385 (m), 1375 (m), 1287 (s), 1113 (m), 1077 (s) cm^{-1}. EIMS: *m*/*z* (%) = 341 (2) [M]$^+$, 144 (43), 129 (71), 107 (21), 91 (100), 79 (17). HRCIMS: calcd. for $C_{19}H_{19}NO_3S$ [M + 1]$^+$ 342.1164; found 342.1168. $C_{19}H_{19}NO_3S$ (341.11): calcd. C 66.84, H 5.61, N 4.10, S 9.39; found C 66.82, H 5.54, N 4.12, S 9.31. The relative configuration of *cis*-**15a** (1*R**,3*S**,6*S**) was corroborated by X-ray crystallographic analysis.[28] Analytical data for *trans*-**15a** (1*R**,3*R**,6*R**): R_f (EtOAc/pentane, 50:50) = 0.19. M.p. 114–115 °C (from CH_2Cl_2/pentane). HPLC (Chiralpak AD, *i*PrOH/hexane, 40:60, 0.7 mL min^{-1}, 230 nm): t_R 12.6 min and 14.7 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 8 H, Ph), 7.23 (d, *J* = 6.6 Hz, 2 H, Ph), 6.35 (dd, *J* = 10.8, 3.6 Hz, 1 H, 4-H), 5.96 (ddd, *J* = 6.8, 4, 1.2 Hz, 1 H, 5-H), 5.17 (AB, *J* = 12.4 Hz, 1 H, Bn), 5.12 (AB, *J* = 12.4 Hz, 1 H, Bn), 4.76 (dd, *J* = 6.8, 1.2 Hz, 1 H, 6-H), 4.48–4.42 (m, 1 H, 3-H), 1.50 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.6 (C=O), 135.4, 134.4, 132.7, 129.1, 129.0, 128.8, 128.7, 128.4, 127.8, 115.2 (5-C), 68.8 (Bn), 65.1 (6-C), 48.6 (3-C), 20.7 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3033 (w), 1723 (s, C=O), 1496 (m), 1455 (m), 1438 (m), 1381 (m), 1264 (s), 1184 (m), 1089 (m), 1058 (m) cm^{-1}. EIMS: *m*/*z* (%) = 341 (0.7) [M]$^+$, 293 (2), 144 (25), 129 (37), 128 (17), 91 (100). HRCIMS: calcd. for $C_{19}H_{19}NO_3S$ [M + 1]$^+$ 342.1164; found 342.1158. $C_{19}H_{19}NO_3S$ (341.11): calcd. C 66.84, H 5.61, N 4.10, S 9.39; found C 66.52, H 5.60, N 4.11, S 9.46. The relative configuration of *trans*-**15a** (1*R**,3*R**,6*R**) was corroborated by X-ray crystallographic analysis.[28] The asymmetric HDA reaction between **1a** and **10**,[17,19] promoted by **4a**-Cu(OTf)$_2$ (100 mol-%) according to the general procedure, afforded exclusively *cis*-**14a**. FC (EtOAc/pentane, 33:67) of the crude product yielded 22.5 mg (31% yield) of *cis*-**14a** as white solid. Analytical data: $[\alpha]_D^{20}$ = +2.6 (*c* = 1.0, CH_2Cl_2). HPLC (Chiralpak AD, *i*PrOH/hexane, 40:60, 0.7 mL min^{-1}, 230 nm): 42% *ee*, t_R 9.5 min (major) and 11.5 min.

3,6-Dihydro-6-methyl-3-phenyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (14b) and 3,6-Dihydro-3-methyl-6-phenyl-2-tosyl-1λ^4,2-thiazine 1-Oxide (15b): The uncatalyzed reaction between *N*-sulfinyl compound **1b** and **10**,[17,19] according to the general procedure, afforded a mixture of *cis*-**14b**, *cis*-**15b**, and *trans*-**15b**. FC (EtOAc/pentane, 33:67 to 50:50) of the crude product yielded 108.9 mg (15% yield) of *trans*-**15b** as a white solid, and a fraction containing a mixture of *cis*-**14b** and *cis*-**15b**. FC (EtOAc/pentane, 20:80) of the latter fraction afforded 363 mg (50% yield) of *cis*-**14b** and 181.5 mg (25% yield) of *cis*-**15b**, both as white solids. Analytical data for *cis*-**14b** (1*R**,3*R**,6*R**): R_f (EtOAc/pentane, 50:50) = 0.29. M.p. 134–136 °C (from CH_2Cl_2/pentane/EtOAc). HPLC (Chiralcel OD-H, *i*PrOH/hexane, 20:80, 0.7 mL min^{-1}, 230 nm): t_R 11.18 min and 15.06 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 2 H, Ph), 7.24 (app. d, *J* = 7.2 Hz, 2 H, Ts), 7.16–7.08 (m, 3 H, Ph), 6.97 (app. d, *J* = 7.2 Hz, 2 H, Ts), 5.93 (dt, *J* = 10.8, 2.8 Hz, 1 H, 4-H), 5.51–5.45 (m, 2 H, 3-H/5-H), 3.55–3.49 (m, 1 H, 6-H), 2.30 (s, 3 H, TsMe), 1.57 (d, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.0, 137.4, 136.9, 130.1 (4-C), 129.6, 129.4, 128.6, 127.9, 127.2, 119.6 (5-C), 60.0 (3-C), 54.4 (6-C), 21.7 (TsMe), 16.3 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3041 (w), 1597 (m), 1493 (m), 1455 (m), 1355 (s), 1164 (s), 1113 (m), 1049 (m), 947 (s) cm^{-1}. EIMS: *m*/*z* (%) = 361 (0.2) [M]$^+$, 219 (2), 217 (25), 129 (100), 91 (100), 65 (31). $C_{18}H_{19}NO_3S_2$ (361.08): calcd. C 59.81, H 5.30, N 3.87; found C 59.76, H 5.24, N 3.89. The relative configuration of *cis*-**14b** (1*R**,3*R**,6*R**) was corroborated by X-ray crystallographic analysis.[28] Analytical data for *cis*-**15b** (1*R**,3*S**,6*S**): R_f (EtOAc/pentane, 50:50) = 0.37. M.p. 137–138 °C (from CH_2Cl_2/pentane/EtOAc). HPLC (Chiralpak AD, *i*PrOH/hexane, 10:90, 1.0 mL min^{-1}, 230 nm): t_R 17.3 min and 19.4 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 (app. d, *J* = 8.4 Hz, 2 H, Ts), 7.43–7.31 (m, 7 H, Ph/Ts), 6.09 (dt, *J* = 10.8, 3.2 Hz, 1 H, 4-H), 5.75 (dt, *J* = 11.2, 2.0 Hz, 1 H, 5-H), 4.68–4.62 (m, 1 H, 3-H), 4.42 (dd, *J* = 5.2, 2.8 Hz, 1 H, 6-H), 2.45 (s, 3 H, TsMe), 1.38 (d, *J* = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.0, 137.4, 136.9, 130.1 (4-C), 129.6, 129.4, 128.6, 127.9, 127.2, 119.6, 60.0 (3-C), 54.4 (6-C), 21.7 (TsMe), 16.3 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3012 (w), 1597 (s), 1493 (m), 1453 (m), 1355 (s), 1166 (s), 1112 (m), 1049 (m), 994 (s), 923 (s) cm^{-1}. EIMS: *m*/*z* (%) = 361 (0.01) [M]$^+$, 219 (4), 217 (53), 171 (12), 155 (95), 144 (93), 143 (44), 129 (100), 128 (89), 91 (99), 65 (50). $C_{18}H_{19}NO_3S_2$ (361.08): calcd. C 59.81, H 5.30, N 3.87; found C 59.70, H 5.24, N 3.89. The relative configura-

tion of *cis*-**15b** (1*R**,3*S**,6*S**) was corroborated by X-ray crystallographic analysis.[28] Analytical data for *trans*-**15b** (1*R**,3*R**,6*R**): R_f (EtOAc/pentane, 50:50) = 0.16. M.p. 131–132 °C (CH_2Cl_2/pentane/EtOAc). HPLC (Chiralpak AD, *i*PrOH/hexane, 40:60, 0.7 mL min^{-1}, 230 nm): t_R 16.4 min and 37.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44–7.32 (m, 5 H, Ph), 7.23 (app. d, J = 8 Hz, 2 H, Ts), 7.10 (d, J = 8 Hz, 2 H, Ts), 6.15 (dd, J = 10.8, 2.8 Hz, 1 H, 4-H), 5.88 (dd, J = 10.4, 6.4 Hz, 1 H, 5-H), 4.80 (d, J = 6.4 Hz, 1 H, 6-H), 4.34–4.31 (m, 1 H, 3-H), 2.39 (s, 3 H, TsMe), 1.40 (d, J = 6.8 Hz, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.4, 136.9, 134.2, 132.5, 129.9, 129.6, 129.3, 129.0, 127.5, 115.4 (5-C), 67.0 (6-C), 49.4 (3-C), 21.8 (TsMe), 19.9 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3012 (w), 1596 (s), 1493 (s), 1451 (s), 1343 (s), 1188 (s), 1162 (s), 1102 (s), 1087 (s), 1042 (m), 922 (s) cm^{-1}. EIMS: *m*/*z* (%) = 219 (1), 217 (13), 155 (50), 144 (61), 129 (100), 91 (81), 65 (14). $C_{18}H_{19}NO_3S_2$ (361.08): calcd. C 59.81, H 5.30, N 3.87; found C 59.73, H 5.13, N 3.88. The asymmetric HDA reaction between **1b** and **10**,[17,19] promoted by **4a**-Cu(OTf)$_2$ (100 mol-%) according to the general procedure, afforded exclusively *cis*-**14b**. FC (EtOAc/pentane, 20:80) of the crude product yielded 90 mg (50% yield) of *cis*-**14b** as white solid. Analytical data: $[\alpha]_D^{20}$ = –36 (c = 1.0, CH_2Cl_2). HPLC (Chiralcel OD-H, *i*PrOH/hexane, 20:80, 0.7 mL min^{-1}, 230 nm): 71% *ee*, t_R 11.18 min and 15.06 min (major).

One-Pot Preparation of Benzyl [(1*R*,4*S*)-4-(Phenylsulfinyl)cyclopent-2-enyl]carbamate (19b) from Cyclopentadiene (17): A solution of the *N*-sulfinyl carbamate **1a** (2.5 mL, 0.496 mmol, 0.2 M) in CH_2Cl_2 was added to the precooled solution of **4a**-Cu(OTf)$_2$ (10 mol-%) at –75 °C. A precooled solution of **17** (100 μL, 0.992 mmol) in CH_2Cl_2 (100 μL) was added to the reaction mixture, followed by TMSOTf (90 μL, 0.496 mmol). The reaction mixture was stirred at –75 °C for 3 h and then added dry methanol (3 mL). The resultant mixture was warmed to room temperature and stirred at this temperature for 4 h. Water (2 mL) was poured into the reaction mixture, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried ($MgSO_4$), passed through a short silica gel column, and the solvent was removed in vacuo. The residue was dissolved in dry THF (5 mL) and cooled to –60 °C. A solution of PhMgBr (1.0 M, 1 mL, 0.992 mmol) in THF was added by syringe, and the resultant mixture was warmed to room temperature overnight. The reaction mixture was hydrolyzed with saturated aqueous NH_4Cl (5 mL) and water (1 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. FC (EtOAc/pentane, 67:33 to 75:25) of the crude provided an inseparable mixture of sulfur epimers **19b** in a ratio of 4:1 (84.6 mg, 50% total yield) as a pale yellow oil. Analytical data of the mixture **19b**: $[\alpha]_D^{20}$ = +201.3 (c = 1.0, CH_2Cl_2). HPLC (Chiralpak AD, *i*PrOH/hexane, 10:90, 1 mL min^{-1}, 230 nm) major epimer: 80% *ee*, t_R 26.4 min (major) and 44.6 min, minor epimer: 16% *ee* t_R 21.5 min and 23.7 min (major). IR (KBr): $\tilde{\nu}$ = 3317 (m, NH), 3033 (w), 1716 (s, C=O), 1513 (s), 1443 (m), 1322 (s), 1234 (s), 1029 (s) cm^{-1}. CIMS: *m*/*z* (%) = 342 (0.04) [M + 1]$^+$, 321 (0.1), 215 (16), 186 (12), 171 (15), 125 (27), 109 (14), 91 (100), 77(10). $C_{19}H_{19}NO_3S$ (341.11): calcd. C 66.84, H 5.61, N 4.10; found C 66.62, H 5.70, N 4.10. Data for major sulfur epimer **19b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.46 (m, 5 H, Ph), 7.40–7.28 (m, 5 H, Ph), 6.16 (m, 1 H, 2-H), 6.02 (d, J = 3.6 Hz, 1 H, 3-H), 5.84 (d, J = 9.6 Hz, 1 H, NH), 5.11 (AB, J = 12.8 Hz, 2 H, Bn), 4.79 (t, J = 8.8 Hz, 1 H, 1-H), 3.80 (m, 1 H, 4-H), 2.16 (dd, J = 15.2, 8.4 Hz, 1 H, 5-H), 1.75 (d, J = 15.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9 (C=O), 142.2, 139.7 (2-C), 137.0, 131.1, 129.5, 128.6, 128.3, 128.2, 128.1 (3-C), 124.2, 71.4 (4-C), 66.5 (Bn), 54.0 (1-C), 29.3 (5-C) ppm.

(3a*R*,6a*S*)-3,3a,4,6a-Tetrahydrocyclopenta[*d*][1,3]oxazol-2-one [(3a*R*,6a*S*)-20]: The title compound was prepared from the mixture of sulfur epimers **19b** (103.0 mg, 0.302 mmol) according to the procedure of Weinreb and co-workers.[8] The crude product was recrystallized from diethyl ether affording (3a*R*,6a*S*)-**20** (24.2 mg, 64% yield) as a white solid. Analytical data for (3a*R*,6a*S*)-**20**: m.p. 116–117 °C (ref.[25] m.p. 117–118 °C). $[\alpha]_D^{20}$ = +5.8 (c = 0.32, $CHCl_3$) {ref.[25] $[\alpha]_D^{20}$ = +7.6 (c = 0.32, $CHCl_3$}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (br. s, 1 H, NH), 6.08–6.06 (m, 1 H, 5-H), 5.87–5.85 (m, 1 H, 6-H), 5.56 (app. d, J = 7.6 Hz, 1 H, 6a-H), 4.45 (app. t, J = 7.3 Hz, 1 H, 3a-H), 2.72–2.64 (m, 1 H, 4-H), 2.47 (m, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C=O), 135.7 (5-C), 128.3 (6-C), 86.3 (6a-C), 53.6 (3a-C), 40.7 (4-C) ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of the chiral ligands **4b** and **5a** and their analytical data.

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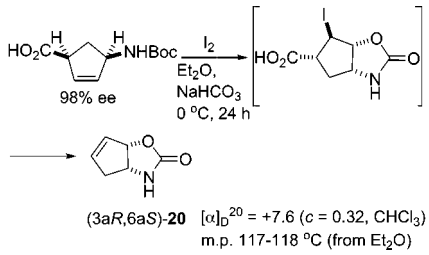

(3a*R*,6a*S*)-**20** $[\alpha]_D^{20}$ = +7.6 (*c* = 0.32, $CHCl_3$)
m.p. 117-118 °C (from Et_2O)

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