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A First Case of Asymmetric Catalysis Induced by Metal-Free Bisoxazolines

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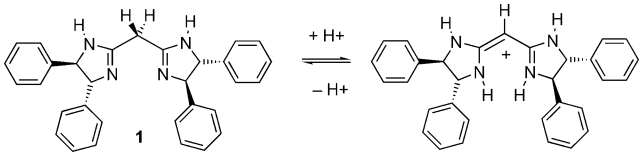
Metal-free bisoxazolines catalyze the Diels–Alder reaction of *N*-substituted maleimides with anthrone derivatives leading to products in excellent yields and enantioselectivities up to 70 %. A mechanism relying on Brønsted-base catalysis is assumed to be involved with formation of an ion pair between the protonated catalyst and the anthrone enolate, which acts as a diene.

Introduction

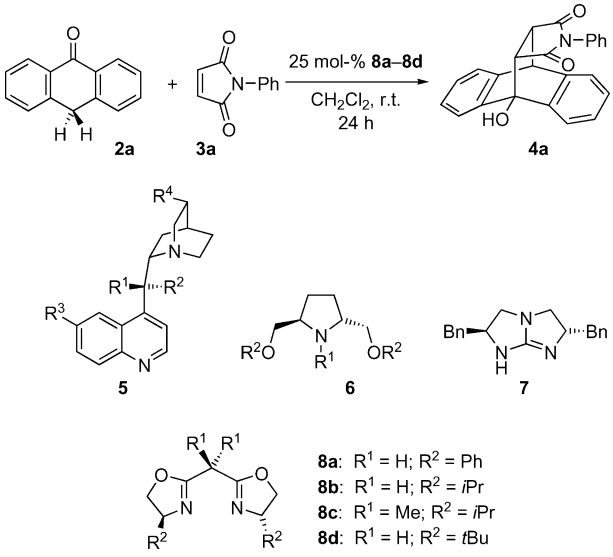
Bisamidine **1**, a new type of chiral base that we have introduced recently, adopts the form of a conjugated enamine-imine tautomer after protonation, resulting in an almost planar structure.[1] Compound **1** thus can play a twofold role in organocatalytic transformations, as a Brønsted-base or, after protonation, as a mild metal-free electrophile (Scheme 1). Base-induced stereoselective transformations mediated by **1** are currently under investigation. The cycloadditions of anthrone **2a** and *N*-alkyl- or *N*-arylmaleimides **3** are well known examples for base-catalyzed Diels–Alder reactions and have been studied extensively.[2] Chiral bases such as cinchona alkaloids **5**,[3] pyrrolidines **6**,[4] and cyclic guanidine **7**[5] have been shown to promote these reactions to give products **4** with moderate to excellent enantioselectivities. Bisamidine **1**, due to its high basicity, is a good catalyst in terms of reaction rates. However, we still have to optimize stereoselectivities.



Scheme 1. Protonation states of chiral bisamidine **1**.[1]

Since their introduction in 1991, C_2-symmetrical bisoxazolines **8** have become one of the most important ligand systems for stereoselective transformations.[6] Starting from amino acids, a large number of compounds with various spacers and side chains can be easily generated. All kinds of metal ions ranging from alkali- to transition metals may then be used to prepare catalytically active chiral complexes. However, to the best of our knowledge, no case of asymmetric catalysis has been described with bisoxazoline ligands acting entirely without coordinated metal-ions.[7]

In spite of the low basicity of bisoxazolines – when compared to bisamidine **1** – the obvious structural analogy of both classes encouraged us to try and catalyze the cycloaddition of anthrones to maleimides with bisoxazolines **8a**–**8d** (Scheme 2).



Scheme 2. Base-catalyzed Diels–Alder reaction of anthrone **2a** and *N*-phenylmaleimide **3a**.

Results and Discussion

Initial experiments started with the Diels–Alder reaction of anthrone **2a** and *N*-phenylmaleimide **3a** in CH_2Cl_2 catalyzed by the bisoxazolines **8a**–**8d**. Due to the low Brønsted-

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basicity of the bisoxazolines, high catalyst loadings of 25 mol-% were required to obtain satisfactory yields. The highest asymmetric induction was observed with the sterically most demanding compound **8d** (Table 1, entry 4). The (*S*,*S*)-configuration could be assigned to the major product enantiomer **4a** by comparison of the optical rotation with literature data.[8] We tested bisoxazoline **8d** in different solvents and found the best results in CH_2Cl_2. In acetonitrile, the cycloaddition yielded entirely racemic material (see Supporting Information). Upon variation of the reaction temperature between –25 and 50 °C, nearly constant enantioselectivities were observed. The best value of 47% *ee* was found at 23 °C (catalyst **8d**, CH_2Cl_2; for details see Supporting Information).

Table 1. Comparison of bisoxazolines as catalysts for the cycloaddition leading to **4a**.

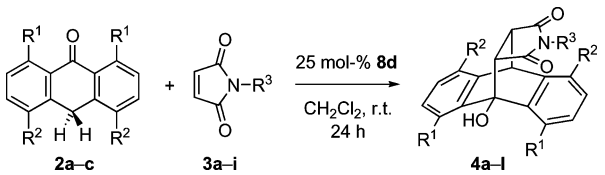
Entry[a]	Catalyst	Yield [%][b]	*ee* [%][c]
1	*ent*-**8a**	60	–3[d]
2	**8b**	71	22
3	**8c**	73	7
4	**8d**	85	47

[a] All reactions were carried out using maleimide **3a** (0.1 mmol), anthrone **2a** (1.1 equiv.) and catalyst (0.25 equiv.) in 1 mL of absol. CH_2Cl_2 at room temperature for 24 h. [b] Isolated yield after column chromatography. [c] Enantiomeric excess was determined by HPLC using Chiralpak IA column. [d] A negative *ee* stands for an excess of *ent*-**4a**.

Using the optimized conditions, we explored the scope of the bisoxazoline-catalyzed Diels–Alder reaction of various *N*-substituted maleimides and different anthrone derivatives. Dienes **2b** and **2c** were prepared by regioselective reductions of 1,8-dichloroanthraquinone.[9] Maleimides **3** are either accessible by Mitsunobu reaction[10] or by addition of the corresponding amine to maleic anhydride followed by an intramolecular ring closure.[11] Both electron-donating and electron-withdrawing substituents were tolerated in R^3 and furnished the products in good to excellent yields and moderate enantioselectivities. Consistent with a Diels–Alder reaction of normal electron demand, the use of the electron-poor anthrone **2b** dropped the yield (Table 2, entry 2). A dramatic increase in enantioselectivity was observed with diene **2c**. The presence of the 1,8-chloro substituents next to the carbonyl function, raised the *ee* value from 40 to 70% (entries 5 and 6). The combination of **2c** and dienophile **3f**, which yielded the highest selectivity in the reaction with unsubstituted anthrone **2a** (entry 8) failed to improve further the level of asymmetric induction (entry 9).

In terms of mechanism, the product **4** may either result from a concerted cycloaddition or a stepwise process via Michael adduct **9** followed by an aldol addition. Michael adducts of type **10** were shown previously to be secondary products resulting from a retro aldol reaction of **4** (Figure 1). They are formed preferentially in protic solvents and were not observed in our study. According to Koerner and Rickborn, all evidence points towards a Diels–Alder mechanism with enolate **2e** acting as a diene.[2a,2b] Stereochemical arguments strengthen the view that enol **2d** is not the relevant

Table 2. Scope of the bisoxazoline-catalyzed Diels–Alder reaction.



Entry[a]	**2** [R^1, R^2]	R^3	Product	Yield [%][b]	*ee* [%][c]
1	**2a** [H, H]	Ph (**3a**)	**4a**	85	47
2	**2b** [H, Cl]	**3a**	**4b**	68	39
3	**2a**	*i*Pr (**3b**)	**4c**	99	43
4	**2a**	*t*Bu (**3c**)	**4d**	92	41
5	**2a**	Cy (**3d**)	**4e**	99	40
6	**2c** [Cl, H]	**3d**	**4f**	94	**70**
7	**2a**	Bn (**3e**)	**4g**	99	40
8	**2a**	$CHPh_2$ (**3f**)	**4h**	87	53
9	**2c**	**3f**	**4i**	94	**67**
10	**2a**	3-F-(C_6H_4)- (**3g**)	**4j**	76	42
11	**2a**	4-Br-(C_6H_4)- (**3h**)	**4k**	67	41
12	**2a**	4-MeO-(C_6H_4)- (**3i**)	**4l**	76	46

[a] All reactions were carried out using maleimide **3** (0.1 mmol), anthrone **2** (1.1 equiv.) and **8d** (0.25 equiv.) in 1 mL of absol. CH_2Cl_2 at room temperature for 24 h. [b] Isolated yield after column chromatography. [c] Enantiomeric excess was determined by HPLC using Chiralpak IA column.

intermediate in the bisoxazoline-catalyzed reactions. In the neutral state, bisoxazolines favour the flexible non-conjugated form characterized by four hydrogen-bond acceptor sites. Enol **2d** may bind weakly to the catalyst as shown in Scheme 3 (left). While this orientation might explain the transfer of chirality, many others also exist. Sampling over all binding modes can hardly explain selectivities up to 70% *ee*.

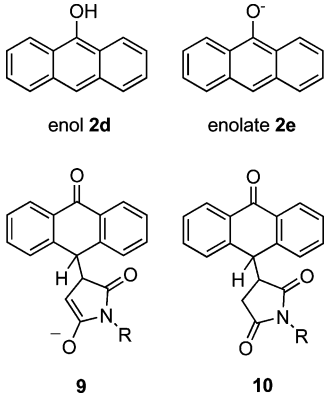
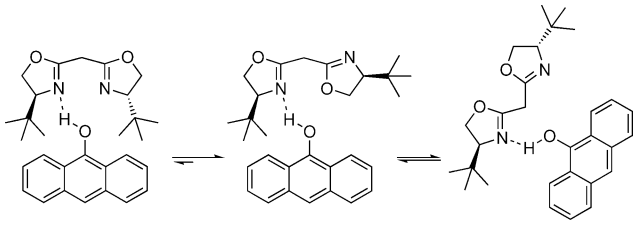


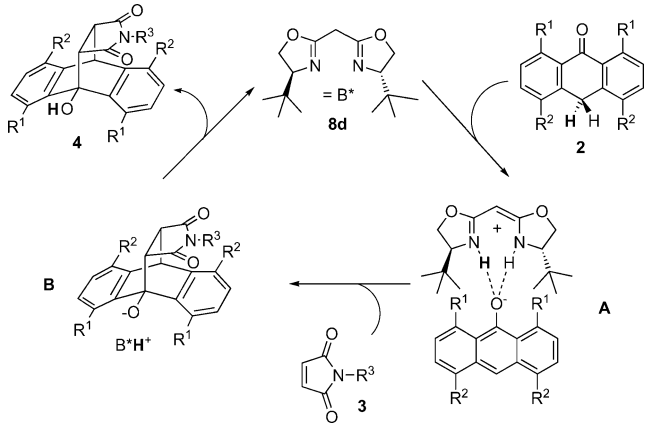
Figure 1. Structures of enol **2d**, enolate **2e**, and of Michael adducts **9** and **10**.

In contrast, the bisoxazolines seem to adopt a planar conjugated form in the monoprotonated state exhibiting two hydrogen-bond donor and two acceptor sites: upon addition of one equivalent of trifluoroacetic acid to compound **8d**, a strong absorption band around 280 nm occurs (see Supporting Information) demonstrating the enamine-imine conjugation, which has been observed previously in bisoxazoline–metal complexes[12] and structurally related



Scheme 3. Some coordination modes of enol **2d** and neutral bisoxazolines.

semicorrins.[13] Photoelectron spectra of neutral bisoxazolines also indicate the presence of conjugated tautomers in the gas phase.[14] This parallels the behaviour of monocationic bisamidine **1** as shown in Scheme 1. The enamine-imine tautomers of protonated catalysts would be excellent hosts to accommodate the oxyanion of enolate **2e** in a contact ion pair stabilized by two hydrogen bonds. The close proximity of the chiral centers to the diene in such complexes could well explain the observed stereoselectivity. When enamine-imine conjugation is prevented by alkyl groups as in bisoxazoline **8c**, the catalyst function is severely impaired (Table 1, entry 3). These data suggest the mechanism depicted in Scheme 4. Acting as a Brønsted base, the bisoxazoline deprotonates the anthrone in the first step. The resulting contact ion pair **A** then allows the transfer of chirality from the catalyst to the product in the subsequent Diels–Alder reaction. The anion of product **4**, a much stronger base compared to the enolate of anthrone **2**, deprotonates **8d**·H^+ upon dissociation of complex **B** thus closing the catalytic cycle. Polar solvents such as acetonitrile are expected to separate ion pair **A** thereby destroying the stereoselectivity of the process (see Supporting Information). UV/Vis spectrometry permits to quantify the extent of deprotonation of anthrone **2a**. In CH_2Cl_2, strong Brønsted bases such as DBU induce an intense orange color by complete conversion of **2a** into its enolate **2e** (see Supporting Information). Triethylamine as a weaker base gives visible color effects only at concentrations above 0.1 M, sufficient to induce complete Diels–Alder reactions of **2a** with maleimides within 15 min.[2a] No color development at all is observed with bisoxazolines. Concentrations



Scheme 4. Proposed catalytic cycle.

of intermediate **A** (Scheme 4) in the reaction mixture thus must be very low, consistent with long reaction times and the need for rather large amounts of catalyst.

Conclusions

In summary, we have developed the first asymmetric catalysis by a bisoxazoline in the absence of any metal ions. With bulky groups in the catalyst and proper substituents in the substrates, good enantioselectivities and excellent yields could be achieved. Since reaction rates correlate with the Brønsted basicity of the catalysts, future experiments will include stronger bases like bisamidines, which will allow a reduction in the amount of catalyst.

Experimental Section

General: NMR: Bruker DPX 250 (^{1}H: 250 MHz; ^{13}C: 63 MHz) or Bruker AM 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz; ^{19}F: 282 MHz). FTIR: Perkin–Elmer 1600 Series. Elemental analysis: Heraeus CHN Rapid. Melting points (uncorrected): Kofler hot-plate microscope. Optical rotation: Perkin–Elmer polarimeter 241. UV spectra: Varian Cary 1E spectrophotometer.

Typical Procedure for Bisoxazoline-Catalyzed Diels–Alder Reactions of Anthrone Derivatives 2 with *N*-Substituted Maleimides 3: *N*-phenylmaleimide **3a** (17.4 mg, 0.1 mmol), anthrone **2a** (21.4 mg, 0.11 mmol) and bisoxazoline **8d** (6.7 mg, 0.025 mmol) were dissolved in 1 mL of absol. CH_2Cl_2 and stirred for 24 h at room temperature. The reaction mixture was purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to afford **4a** as a colorless crystalline solid.

4a: Yield 31.1 mg, 85%; m.p. 199–201 °C (lit. 208–209 °C).[4a] $[\alpha]_D^{20}$ = +24.6 (*c* = 1.15, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.28 (d, *J* = 8.5 Hz, 1 H, C*H*-COH), 3.49 (dd, J_1 = 3.6, J_2 = 8.6 Hz, 1 H, CH-C*H*-CH), 4.54 (s, 1 H, O*H*), 4.84 (d, *J* = 3.5 Hz, 1 H, C*H*-CH-CH-COH), 6.45–6.52 (m, 2 H, aryl-*H*), 7.20–7.36 (m, 8 H, aryl-*H*), 7.40–7.43 (m, 1 H, aryl-*H*), 7.55–7.58 (m, 1 H, aryl-*H*), 7.72–7.75 (m, 1 H, aryl-*H*) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 44.79, 47.66, 50.78, 77.30, 120.88, 121.09, 123.76, 124.69, 126.26, 126.84, 126.92, 127.24, 127.35, 128.97, 129.11, 130.86, 136.62, 138.83, 140.92, 142.26, 175.59, 177.11 ppm. IR (KBr): $\tilde{\nu}$ = 3416 (m), 3070 (w), 2961 (w), 1773 (w), 1699 (s), 1596 (w), 1494 (m), 1458 (m), 1381 (s), 1296 (w), 1266 (w), 1245 (w), 1175 (s), 1136 (w), 1073 (w), 1056 (w), 1028 (w), 990 (w), 962 (w), 946 (w), 922 (w), 846 (w), 786 (w), 770 (s), 756 (m), 724 (w), 690 (w) cm^{-1}. $C_{24}H_{17}NO_3$ (367.40): calcd. C 78.46, H 4.66, N 3.81; found C 78.40, H 4.73, N 3.61. HPLC conditions: CHIRALPAK IA column (250 × 4.6 mm), *n*-hexane/propan-2-ol/CH_2Cl_2 (64:19:17), flow-rate 0.7 mL min^{-1}, t_{major} = 10.5 min, t_{minor} = 12.0 min, 47% *ee*.

The racemic compound was prepared with triethylamine (10 μL) instead of bisoxazoline. After 30 min the crude product was also purified by flash column chromatography.

Supporting Information (see also the footnote on the first page of this article): Characterisation data for Diels–Alder adducts **4**; results for optimal reaction conditions. UV spectra of **2a** and **8d** and copies of chromatograms obtained with chiral columns.

Acknowledgments

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