Abstract

$C_2$-symmetric bisamidines 8 have been tested as chiral Brønsted bases in the Diels-Alder reaction of anthrones and $N$-substituted maleimides. High yields of cycloadducts and significant asymmetric inductions up to 76% ee are accessible. The proposed mechanism involves proton transfer between anthrone and bisamidine, association of the resulting ions and finally a cycloaddition step stereoselectively controlled by the chiral ion pair.

Introduction

The cycloadditions of anthrones 1 and $N$-substituted maleimides 2 are prominent examples of asymmetric catalysis exerted by chiral Brønsted bases. Moderate to excellent stereoselectivities of products 3 have been reported using pyrrolidines 4 [1,2], cyclic guanidine 5 [3], or cinchona alkaloids 6 [4] as catalysts. Recently, we could promote this type of cycloaddition by metal-free bisoxazolines 7 in up to 70% ee, in spite of their limited Brønsted-basicity [5] (Scheme 1).

Our study was motivated by the structural similarity of bisoxazolines 7 and bisamidines 8. Bisamidines 8, readily accessible from malonodinitrile in two steps, prefer the conjugated tautomeric form (enamine-imine) in the monoprotonated state, which is characterised by an almost planar structure [6] (Scheme 2).

The aqueous $pK_a$ of 8·H$^+$ is approximately 11, sufficient to allow deprotonation of anthrones 1 ($pK_a$ around 10, [7,8]) by bisamidines to a significant extent. Here we report on the use of neutral bisamidines 8 as asymmetric Brønsted base catalysts in the cycloaddition of anthrones 1 and maleimides 2.

Results and Discussion

Analogous to the synthesis of compound 8a [6], the other bisamidines were prepared as hydrochlorides in 60–79% yield from the corresponding chiral diamines 9 and bisimidate 10 in refluxing ethanol. Simple extraction in the presence of Na$_2$CO$_3$ afforded the neutral bases 8b–c and ent-8d in almost quantitative yield. The $S,S$ configured diamines 9b and 9c were prepared from L-(+)-tartaric acid ($R,R$) via the vicinal diazide using Saalfrank’s procedure [9]. 9d was purchased as the
Scheme 1: Diels-Alder reaction of anthrones 1 and maleimides 2 catalyzed by chiral Brønsted bases 4–8.

Scheme 2: Protonation states and tautomerism of C₂-symmetric bisamidine 8a [6].

dihydrochloride salt and then deprotonated by aqueous sodium hydroxide. As an “artefact” of the sequence rule, the S,S-configurated diamine 9d leads to bisamidine ent-8d (Scheme 3).

The anthrones 1b (R¹: H; R²: Cl) and 1c (R¹: Cl; R²: H) resulted from regioselective reductions of 1,8-dichloroanthraquinone [10,11]. Aliphatic side chains of compounds 2 could be introduced by a Mitsunobu alkylation of maleimide [12]. Alternatively, substituted maleimides were prepared by reaction of maleic anhydride with the corresponding amines followed by ring closure [13,14].

 Cycloaddition kinetics of 1a and 2a was examined first by ¹H NMR in CD₂Cl₂ at room temperature. In the absence of catalyst, no product could be observed after 4 days. 5 mol% of the bisamidinium salt 8a·H⁺ with tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (TFPB⁻) as weakly coordinating anion resulted in 7% yield of 3a after 4 h. In contrast, only 1 mol% of the free Brønsted base 8a led to a high rate increase in the first 30 min. After 90 min no further conversion was observed indicating product inhibition (Figure 1). Accordingly, the reaction runs best in the base-catalyzed mode. Compared to the bisoxazolines 7, bisamidines 8 as stronger Brønsted bases induced much higher rates in all subsequent experiments.

In the next series of experiments, bisamidines 8a–c and ent-8d were compared as catalysts of the cycloaddition forming 3a from N-phenylmaleimide (2a) and anthrone (1a). Using 0.25 equiv of catalyst at room temperature, isolated yields between 71% and 86% were obtained after 30 min. The best enantioselectivity, albeit low, was induced by amidine 8c (24% ee). As expected, in the presence of catalyst ent-8d product ent-3a was formed preferentially (Table 1).

In a solvent screening using 10 mol% of TBDPS-protected bisamidine 8c, best results were obtained in dichloromethane (84% yield; 30% ee). Even higher yields were accessible in aromatic solvents, however, at the price of reduced stereoselectivity (Table 2).

Lowering the reaction temperature from 23 to −20 °C (8c, dichloromethane) retarded the cycloaddition but did not change enantioselectivities. After extended reaction times, excellent yields were still observed. Up to 39% ee was finally obtained at −70 °C. However, such conditions resulted in lower yields, even with increased catalyst loads and further extended reac-
Scheme 3: Synthesis of C$_2$-symmetric bisamidines 8b–c and ent-8d.

Table 1: First evaluation step of chiral bisamidine catalysts.

| entry$^a$ | catalyst | yield [%]$^b$ | ee [%]$^c$ |
|-----------|----------|---------------|------------|
| 1         | 8a       | 86            | 11         |
| 2         | 8b       | 78            | 17         |
| 3         | 8c       | 85            | 24         |
| 4         | ent-8d   | 71            | -17$^d$    |

$^a$All reactions were carried out using 0.1 mmol maleimide 2a, 1.1 equiv anthrone (1a) and 0.25 equiv of catalyst in 1 mL abs. dichloromethane at room temperature for 30 minutes. $^b$Isolated yield after column chromatography. $^c$The enantiomeric excess was determined by HPLC using a Chiralpak IA column. $^d$A negative ee stands for an excess of ent-3a.

Having identified suitable experimental conditions, we explored the scope of the bisamidine-catalyzed Diels-Alder reaction. The results are summarized in Table 4. Both electron-donating and electron-withdrawing substituents were tolerated and furnished products in good to excellent yields and with moderate values of ee. A remarkable increase in enantioselectivity was observed using maleimide 2i. The steric hindrance imposed by the large 2,6-diisopropylphenyl moiety of 2i resulted in 76% ee at −70 °C but also lowered reaction rates.

Only 13% yield could be obtained under such conditions. Yields rose to 65% at room temperature (51% ee; entries 11 and 12). With other sterically hindered dienophiles such as N-tert-
butylnmaleimide (2e), the level of ee remained low (entry 4). The halogen-substituted anthrones 1b–c did not react with 2i at −70 °C. At room temperature, however, 1b and 2i were efficiently transformed into 3m by catalyst 8a with 76% yield and 54% ee. A single recrystallisation step afforded an almost enantiopure product (96% ee). The R,R configuration of compound 3m was determined by anomalous X-ray diffraction using a single crystal of 3m with 96% ee (Figure 2).

A mechanistic rationalisation is proposed in Scheme 4. The catalyst deprotonates the anthrone in the initial step. This assumption is supported by the pKₐ values of compounds 2a (10, [7,8]) and 8b (−11, [6]). Furthermore, the appearance of the yellow color of enolates (1·H⁺) shows significant proton transfer when bisamidine 8a is added to anthrones 1a, 1b, or 1c. A chiral contact ion pair A is formed and controls the stereochemical course of the Diels-Alder reaction with maleimides. In the last step, the catalyst-product-complex B dissociates and regenerates the unprotonated bisamidine.

| Table 2: Influence of the solvent on the bisamidine catalyzed Diels-Alder reaction. |
|------|------|------|
| entry | solvent                  | yield [%] | ee [%] |
| 1     | dichloromethane           | 84       | 30    |
| 2     | chloroform                | 86       | 18    |
| 3     | benzene                   | 98       | 21    |
| 4     | toluene                   | 99       | 16    |
| 5     | o,o,o-trifluorotoluene    | 99       | 13    |
| 6     | dibutyl ether             | 89       | 11    |

aAll reactions were carried out using 0.1 mmol maleimide 2a, 1.1 equiv anthrone (1a) and 0.1 equiv of 8c in 1 mL abs. solvent at room temperature for 60 minutes. bIsolated yield after column chromatography.

cThe enantiomeric excess was determined by HPLC using a Chiralpak IA column.

| Table 3: Influence of temperature on the Diels-Alder reaction. |
|------|------|------|------|------|------|
| entry | reaction temperature [°C] | reaction time [h] | yield [%] | ee [%] |
| 1     | 23   | 1    | 84   | 30   |
| 2     | 0    | 24   | 96   | 29   |
| 3     | −20  | 24   | 98   | 31   |
| 4     | −40  | 48   | 96   | 36   |
| 5     | −70  | 96   | 71   | 39   |

aAll reactions were carried out using 0.1 mmol maleimide 2a, 1.1 equiv anthrone (1a) and 0.1 (entry 1–4) or 0.25 equiv (entry 5) of 8c in 1 mL abs. dichloromethane. bIsolated yield after column chromatography.

cEnantiomeric excess was determined by HPLC using Chiralpak IA column.

Table 4: Scope of the Diels-Alder reaction.

| entry | 1 [R₁, R₂] | R₃ | condition | 3 | yield [%] | ee [%] |
|------|------------|----|-----------|---|-----------|-------|
| 1    | 1a [H, H₃] | Ph | (2a)      | A | 3a        | 96    | 36    |
| 2    | 1b [H, Cl] | 2a | A         | 3b | 95        | 41    |
| 3    | 1a          | iPr | (2b) | B | 3c        | 74    | 26    |
| 4    | 1a          | t-Bu | (2c) | B | 3d        | 45    | 30    |
| 5    | 1a          | Cy | (2d) | B | 3e        | 83    | 42    |
| 6    | 1c [Cl, H]  | 2d | B         | 3f | 90        | 19    |
| 7    | 1a          | Bn | (2e) | A | 3g        | 95    | 20    |
| 8    | 1a          | CHPh₂ | (2f) | A | 3h        | 85    | 26    |
| 9    | 1a          | 4-Br-(C₆H₄)- (2g) | B | 3i | 70        | 13    |
| 10   | 1a          | 4-MeO-(C₆H₄)- (2h) | A | 3j | 82        | 32    |
| 11   | 1a          | 2,6-IPr-(C₆H₅)- (2l) | B | 3k | 13        | 76    |
| 12   | 1a          | 2i | C         | 3k | 65        | 51    |
| 13   | 1c          | 2i | C         | 3l | 77        | 34    |
| 14   | 1b          | 2i | C         | 3m | 76        | 54    |

aAll reactions were carried out using 0.1 mmol maleimide, 1.1 equiv anthrone in 1 mL abs. CH₂Cl₂. bA = 10 mol% 8c, −40 °C, 48 h; B = 25 mol% 8a, −70 °C, 96 h; C = 25 mol% 8a, −30 °C, 54 h; D = 10 mol% 8c, 3 h. cIsolated yield after column chromatography. dThe enantiomeric excess was determined by HPLC using a Chiralpak IA column. eRecrystallized from 2-propanol/n-hexane.
**Conclusion**

C$_2$-symmetric bisamidines were shown to be potent chiral Brønsted base catalysts for the Diels-Alder reaction of N-substituted maleimides and anthrones. Compared to bisoxazolines 7, much shorter reaction times under comparable conditions were sufficient with the more basic bisamidine catalysts 8 (~50-fold [5]). The higher intrinsic reactivity of the bisamidines allowed to run the reactions at lower temperatures. In both groups of catalysts, the phenyl substituted species induced the lowest enantioselectivities. Bisamidine 8a performed better than the corresponding bisoxazoline. Increasing the size of substituents in catalysts 8b–d also improved stereoselectivities, but not to high levels. This may be due to the flexible nature of the substituents present in bisamidines 8b and 8c. It is instructive, therefore, to compare with the bisoxazolines 7. By far the best enantioselectivities were observed in this series with the t-Bu derivative (47% ee versus 3% for the phenyl analogue in the reaction of 1a and 2a). Keeping in mind that even the less selective bisamidine 8a could induce up to 76% ee in favorable cases, replacing the phenyl moieties of 8a by t-Bu is an attractive option for future studies on bisamidine-mediated organocatalytic transformations.

**Supporting Information**

**Supporting Information File 1**

Supporting information features characterisation data and copies of $^1$H- and $^{13}$C-NMR spectra of anthrones 1, maleimides 2, Diels-Alder adducts 3, bisamidine hydrochlorides 8b–d·H$^+$·Cl$^-$, neutral bisamidines 8b–d and diamines 9b–c, plus copies of chromatograms obtained with chiral columns.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-28-S1.doc](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-28-S1.doc)

**Supporting Information File 2**

X-Ray data of compound 3k

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-28-S2.cif](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-28-S2.cif)

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**Scheme 4:** Proposed mechanism of the Diels-Alder reaction.
Supporting Information File 3
X-Ray data of compound 3m
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-28-S3.cif]

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