Facile conversion of 1,2-dicyanobenzene into chiral bisamidines

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Abstract

Nucleophilic catalysis by N-acetyl cysteine permits the smooth reaction of 1,2-diarylethylene-1,2-diamines with 1,2-dicyanobenzene forming chiral bisamidines in yields up to 94% in a single step. Such bisamidines can be used as Brønsted bases or, in the protonated state, as electrophilic catalysts to promote Diels-Alder reactions with medium levels of enantioselectivity.

Keywords: Anthrone, BArF4 salts, Dane’s diene, organocatalysis, steroid skeleton, thiol catalysis
Introduction

Chiral amidines and guanidines are versatile compounds that have been applied many times in studies on molecular recognition\(^1\)-\(^6\) and enantioselective catalysis.\(^7\)-\(^24\) Our group, for example, has introduced the bisamidines \(1\) and \(2\) (Figure 1).\(^{25,26}\) In the protonated state, these compounds promote Diels-Alder reactions as electrophilic catalysts.\(^27\) The geometry of compound \(1\) was designed to coordinate cyclic 1,2 diketones, carboxylates, or nitronates by hydrogen bonds.\(^{25}\) The monocation of compound \(2\), in contrast, has NH groups converging towards a single carbonyl oxygen.\(^26\) It is a weaker electrophile compared to the dication of \(1\). A second protonation of \(2\) occurs at the central carbon, a formal enamine. C-protonation interrupts conjugation and is thermodynamically unfavorable. Accordingly, the dication of \(2\) tends to react as a Brønsted acid. The chiral guanidine \(3\) has been used for enantioselective Brønsted base catalyzed reactions.\(^28\)

![Figure 1. Structures of the chiral bisamidines 1 and 2 and of the guanidine 3.](image)

In the current study, we describe a one-step synthesis of bisamidines characterized by the general structure \(6\) (Figure 2). N-permethylated analogs of \(6\) have been previously described by Wilhelm.\(^{23,24}\) However, the cyclic amidines were prepared in a different way from aldehydes and diamines by subsequent oxidation of the aminal.\(^{19,20,29}\) Compared to compound \(1\), the new bisamidines are based on a 1,2-phenylene linker bringing the nitrogens closer together as in compound \(2\). However, due to a lack of direct conjugation, the bisamidines \(6\) can be doubly protonated without problems and isolated as their chloride or tetraaryl borate salts. Two preliminary examples show how the compounds may be used as chiral Brønsted bases or, in the dicationic states, as electrophilic catalysts.

![Figure 2. Preparation of bisamidines 6a-e from phthalonitrile 4. 5a/6a: Ar = Ph, R,R enantiomer (94% of 6a after 22 h); 5b/6b: Ar = 2-hydroxyphenyl, R,R enantiomer (64% of 6b after 8 h reflux + 15 h r.t.); 5c/6c: Ar = 2-naphthyl, S,S enantiomer (20% of 6c after 26 h); 5d/6d: Ar = p-biphenyl, S,S enantiomer (65% of 6d after 25 h); 5e/6e: Ar = 1-naphthyl, S,S enantiomer (36% of 6e after 37 h). Numbers 7a-e refer to the hydrochlorides of 6a-e and 8a-e to the BAr\(^{4}\) salts.](image)
Results and Discussion

The obvious starting material for the synthesis of bisamidines 6 is 1,2-dicyanobenzene 4 (Figure 2). This compound, however, has a tendency to form phthalocyanines. In the presence of NaOMe, for example, we observed the formation of dark blue solutions. To avoid such byproducts, we used N-acetyl cysteine as a nucleophilic catalyst. In the presence of 1.2 equivalents of this thiol, the conversion of 4 into bisamidine 6a can be achieved in 94% yield simply by refluxing with 2.2 equivalents of diamine 5a in dry methanol. No colored byproducts are formed. The yield of bisamidines however drops with increasing steric demand of the diamines (Figure 3). While diamines 5a and 5b are commercial compounds, 5c-e had to be prepared by stereoselective reactions. In the present study, we have applied the method of Chin based on a [3,3]-sigmatropic rearrangement of bisimines formed from aldehydes and (R,R)-diamine 5b yielding the (S,S)-configurated products 5c-e.

Figure 3. Structures of bisamidines 6a-e and yields when prepared from phthalonitrile 4 and bisamines 5a-e.

Crystals of high quality could be obtained by slow diffusion of n-pentane into a solution of bisamidine 6a in EtOAc. The crystal structure (Figure 4 and Supporting Information) shows the close proximity of the
amidine nitrogens that, in the doubly protonated form, may accommodate and activate a carbonyl guest molecule.

Figure 4. Crystal structure of bisamidine 6a.

Initially we speculated the OH groups present in bisamidine 6b might form additional hydrogen bonds with a substrate thus causing increased electrophilic activation. NMR evidence, however, does not support this idea: The NH signals of the other bisamidines in DMSO appear around 8.50 ppm and shift to 12.0 ppm upon protonation with HCl. In the 2-hydroxyphenyl analog, the NH signal moves from 9.61 (6b) to 11.26 ppm (7b). Interestingly, bisamidine protonation also induces a major shift of the OH signal from 3.17 (6b) to 10.28 ppm (7b) indicating hydrogen bonds between NH as donor and OH as acceptor. A similar type of intramolecular H-bonds is well known from TADDOLs. Thus, in contrast to other bisamidine hydrochlorides and BArF4 salts, OH but no longer NH groups are expected to act as H-bond donors in the 2-hydroxyphenyl analogs 7b and 8b.

The Diels-Alder reaction of Dane’s diene 9 and diketone 10 has been suggested decades ago as a synthetic approach towards steroids (Figure 5). Depending on solvents, the cycloaddition may preferentially form the constitutional isomers rac-13 or rac-14 which slowly tautomerize forming compounds rac-15 and rac-16. In the presence of chiral Lewis acids, isomer 13 can be obtained with excellent constitutional and enantioselectivity. This reaction represents the key step in one of the total syntheses of estrone. Hydrogen bond mediated association of diketone 10 to amidinium ions also accelerated the cycloaddition with Dane’s diene and low to medium levels of enantioselective control were observed in the presence of chiral amidines. The BArF4 salt of bisamidine 1 (100 mol %) for example selectively formed the correct constitutional isomer ent-15 with ee values ranging from 14% at 5 °C, 25% at -16 °C and up to 47% at -70 °C. Using a specifically designed axially chiral amidine, the reaction could be further optimized yielding 24% for the complete multistep synthesis from Dane’s diene 9 to enantiopure (+)-estrone. In the present study, we have repeated this well established reaction in the presence of BArF4 salt 8a (20 mol %): In toluene at -20 °C diketone ent-13 was formed in 65% yield with 28% ee. This result comes close to the selectivities observed for bisamidine 1. However, it is clearly inferior to the variant using the axially chiral amidine.
Cycloadditions of Dane’s diene and compounds 11 and 12 are further options to synthesize (+)-estrone from diene 9. Both reactions can be catalyzed with excellent stereoselectivities by protonated chiral oxazaborolidines.\textsuperscript{41,42} Although mono carbonyl groups should nicely fit into the cationic cleft of BAr\textsuperscript{6} salt 8a, we could not detect any product from the reaction of 9 and 11. Similarly, even after 3 days at 40 °C (10 mol % 8a, CH\textsubscript{2}Cl\textsubscript{2}) not more than 9% of the racemic cycloadduct could be isolated from a test reaction of 9 and cyclopentenone 12. Thus, in comparison to protonated oxazaborolidines, the bisamidinium salts seem to be less potent electrophilic catalysts.

\[
\text{9 + 10} \rightarrow \text{13 + ent-13 + 14 + ent-14} \rightarrow \text{15 + ent-15 + 16 + ent-16}
\]

\textbf{Figure 5.} Dane’s diene 9 and dienophiles 10 – 12 previously used in total syntheses of estrone.

\textbf{Figure 6.} The enolate of anthrone 17 reacts in a Brønsted base induced cycloaddition with dienophile 18.
Deprotonation of anthrone 17 forms an electron rich diene which readily undergoes Diels-Alder reactions with dienophils such as 18 (Figure 6). When conducted with a chiral Brønsted base in nonpolar solvents, chiral ion pairs are formed and the cycloaddition can show high levels of enantioselectivity. We have previously used this reaction to evaluate the chiral guanidine 3 and observed ee values of product 19 around 30%. Based on this protocol, we have now tested bisamidine 6a. In the presence of 10 mol % of 6a in THF, 86% of product 19 with 46% ee could be isolated. No subsequent base induced retro aldol reaction occurred as observed in the presence of guanidine 3. The ee of product 19 increased to 84% upon recrystallization.

Conclusions

By nucleophilic catalysis with N-acetyl cysteine, the conversion of 1,2-dicyano benzene 4 into chiral bisamidines becomes a simple and effective procedure. Recent advances in the synthesis of enantiopure 1,2-disubstituted ethylene-1,2-diamines further increase the usefulness of this method. The resulting products 6a-e have some potential as chiral Brønsted bases. When converted into salts with non-coordinating counterions, BAr^+ salts 8a-e can also play a role as chiral hydrogen bond donors. Like Lewis acids, they can activate substrates for Diels-Alder reactions. However, they are clearly less potent as protonated oxazaborolidines. Furthermore, bisamidines 1 and 6 may be of interest as chiral ligands in coordination chemistry.

Experimental Section

General. Column chromatography: silica gel (60 Å pore size, 0.04-0.063 mm particle size). Proton nuclear magnetic resonance (1H NMR) and carbon nuclear magnetic resonance spectra (13C-NMR) were recorded with Bruker AV 250 (1H: 250 MHz) or Bruker AV 300 (1H: 300 MHz; 13C: 75.5 MHz) or Bruker AV 500 (1H: 500 MHz; 13C: 125.8 MHz) NMR spectrometers. Chemical shifts for protons are reported in parts per million (δ scale) and internally referenced to the proton resonances of the solvent (CDCl3: δ 7.26, d6-DMSO: δ 2.50). Chemical shifts for carbon are reported in parts per million (δ scale) and referenced to the carbon resonances of the solvent (CDCl3: δ 77.00, d6-DMSO: δ 39.51). Data are represented as follows: chemical shift, multiplicity (s singlet, bs broad singlet, d doublet, t triplet, q quartet, m multiplet, dd double doublet), coupling constants in Hz, and integration. ESI-MS spectra were obtained on a Fisons VG Plattform II. HRMS spectra were recorded on a MALDI LTQ Orbitrap mass spectrometer from Thermo Scientific.

1,2-Bis((4R,5R)-4,5-diphenyl-4,5-dihydro-1H-imidazol-2-yl)-benzene (6a). To a solution of phthalonitrile 4 (169 mg, 1.32 mmol, 1.0 equiv.) and N-acetyl cysteine (258 mg, 1.58 mmol, 1.2 equiv.) in dry methanol (20 mL) at rt (argon atmosphere) was added (1R,2R)-1,2-diphenylethlenediamine 5a (618 mg, 2.91 mmol, 2.2 equiv.). The solution was stirred at rt for 2 h and then heated to reflux for 22 h. After the mixture was cooled to rt, the solution was evaporated under reduced pressure and the residue purified by silica gel chromatography (EtOAc/MeOH 10:1 + 1% NEt3) to give 6a as a colourless solid (645 mg, 1.24 mmol, 94%). Rf 0.29 (EtOAc/MeOH 10:1 + 1% NEt3); mp 210 – 212 °C; [α]D20 +174 (c 1.0, MeOH); 1H NMR (500 MHz, DMSO-d6, δ): 8.27 (bs, 2 H, exchange with D2O), 7.91-7.89 (m, 2 H), 7.65-7.63 (m, 2 H), 7.30-7.23 (m, 20 H), 4.71 (broad, 4 H); 13C NMR (126 MHz, DMSO-d6, δ): 164.1, 143.9, 130.8, 129.9, 129.8, 128.5, 127.2, 126.6, 79.9, 69.5; MS (ESI, m/z):...

(4R,4'R,5R,5'R)-2,2'-((1,2-Phenylene)bis(4,5-diphenyl-4,5-dihydro-1H-imidazol-3-im) chloride (7a). To a solution of bisamidine 6a (0.62 g, 1.20 mmol, 1.0 equiv.) in dry CH₂Cl₂ (20 mL) at rt (argon atmosphere) was added hydrogen chloride solution (1.26 mL, 2.52 mmol, 2.1 equiv., 2.0 M in Et₂O). The clear solution was stirred at rt for 1.5 h, evaporated under reduced pressure and dried in vacuo to obtain 7a as a yellow solid (0.71 g, 1.20 mmol, quant.). ¹H NMR (300 MHz, DMSO-d₆, δ): 11.43 (bs, 4 H), 8.19 (bs, 2 H), 8.12 (bs, 2 H), 7.68 (bs, 8 H). ¹³C NMR (75 MHz, DMSO-d₆, δ): 163.6, 160.9 (q, J₁₁₈₋₁₃C 49.2 Hz, Barf₄), 136.8, 134.0 (Barf₄), 132.0, 129.0, 128.4 (qq, J₁₃C₋₁₉F 31.6, 2.8 Hz, Barf₄), 127.7, 124.0 (q, J₁₃C₋₁₉F 272.5 Hz, peaks at 129.4, 125.8, 122.2, 118.6, Barf₄), 117.6 (septet, J₁₃C₋₁₉F 3.6 Hz, Barf₄).

1,2-Bis((4R,5R)-4,5-di-(2'-hydroxyphenyl)-4,5-dihydro-1H-imidazol-2-yl)benzene (6b). To a solution of phthalonitrile 4 (227 mg, 1.77 mmol, 1.0 equiv.) and N-acetyl cysteine (344 mg, 2.11 mmol, 1.2 equiv.) in dry methanol (30 mL) at rt (argon atmosphere) was added bis(trifluoromethyl)phenylborate (2.07 g, 2.34 mmol, 2.0 equiv.). The clear solution was stirred at rt for 1.5 h and evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with brine and the aqueous phase was extracted several times with CH₂Cl₂. The combined organic phase was dried over Na₂SO₄, evaporated under reduced pressure and dried in vacuo to obtain 6b as a yellow solid (305 mg, 1.12 mmol, 64%). ¹H NMR (500 MHz, DMSO-d₆, δ): 6.75 (dd, J 7.7, 1.7 Hz, 4 H), 5.48 (bs, 4 H); ¹³C NMR (126 MHz, DMSO-d₆, δ): 163.3, 150.9 (q, J₁₁₈₋₁₃C 46.1 Hz, Barf₄), 139.0 (Barf₄), 135.1 (Barf₄), 127.7, 124.0 (q, J₁₃C₋₁₉F 272.5 Hz, peaks at 129.4, 125.8, 122.2, 118.6, Barf₄), 117.6 (septet, J₁₃C₋₁₉F 3.6 Hz, Barf₄).

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aqueous phase was extracted several times with CH₂Cl₂. The combined organic phase was dried over Na₂SO₄, evaporated under reduced pressure and dried in vacuo to obtain 8b as colourless foam (2.17 g, 0.94 mmol, 96%). §H NMR (300 MHz, DMSO-d₆, δ): 11.00 (s, 4 H), 10.07 (s, 4 H), 8.07-8.04 (m, 2 H), 7.94-7.91 (m, 2 H), 7.70 (bs, 8 H), 7.62 (bm, 16 H), 7.38 (dd, J 7.6, 1.4 Hz, 4 H), 7.24 (td, J 7.2, 1.5 Hz, 4 H), 6.93 (dd, J 8.1, 0.8 Hz, 4 H), 6.84 (td, J 7.3, 0.7 Hz, 4 H), 5.52 (s, 4 H); ¹³C NMR (75 MHz, DMSO-d₆, δ): 162.9, 161.0 (q, J₁¹C-⁻⁻⁻⁷BArF₄), 155.6, 134.0 (BArF₄), 133.4, 130.1, 130.0, 129.1, 128.5 (qq, J₁³C-⁻⁻⁻⁷BArF₄), 124.7, 124.0 (q, J₁³C-⁻⁻⁻⁷BArF₄) 272.8 Hz, peaks at 129.4, 125.8, 122.2, 118.6, BARF₄), 123.6, 119.3, 117.5 (septet, J₁¹C-⁻⁻⁻⁷BARF₄, 3.4 Hz, BARF₄), 115.8, 64.6; §F NMR (471 MHz, DMSO-d₆, δ): -61.86; MS (ESI, m/z): [M + H]+ 583.20; MS (ESI, m/z): 863.26 [(BARF₄)]; HRMS (MALDI, m/z): [M + H]+ calcld for C₃₉H₃₁N₄O₆, 583.23398, found, 583.23443.

(1S,2S)-1,2-Di(naphthalen-2-yl)ethane-1,2-diammonium chloride (5c · 2 HCl). To a solution of (R,R)-1,2-bis-(2-hydroxyphenyl)-1,2-diamino-ethane 5b (1.22 g, 4.99 mmol, 1.00 equiv.) in DMSO (25 mL) was added naphthalene 2-carbaldehyde (1.87 g, 11.97 mmol, 2.40 equiv.), then stirred for 19 h at rt and then water (75 mL) and Et₂O were added. The phases were separated, the combined organic layers were dried over Na₂SO₄ and evaporated under reduced pressure. The orange solid residue was dissolved in THF (70 mL) and concentrated HCl (37%, 1.5 mL) was added. The reaction mixture was stirred for 19 h, the precipitate was filtered off and washed with cold THF. The residue was dried in vacuo to afford the hydridochloride of 5c as a colourless solid (1.40 g, 3.63 mmol, 73%). mp 245 – 246 °C; §H NMR (300 MHz, DMSO-d₆, δ): 9.50 (bs, 6 H), 8.00 (d, J 1.1 Hz, 2 H), 7.83-7.75 (m, 6 H), 7.55 (dd, J 7.8, 1.7 Hz, 2 H), 7.51-7.45 (m, 4 H), 5.42 (bs, 2 H); ¹³C NMR (75 MHz, DMSO-d₆, δ): 132.7, 132.2, 130.7, 128.8, 128.1, 127.9, 127.5, 126.9, 126.6, 125.5, 56.9; MS (ESI, m/z): 296.14 [M + H⁺ – NH₃]; HRMS (MALDI, m/z): [M + H⁺ – NH₃] calcld for C₂₂H₁₈N, 296.14338; found 296.14301.

(1S,2S)-1,2-Di(naphthalen-2-yl)ethane-1,2-diamine (5c). A suspension of 5c · 2 HCl (1.21 g, 3.14 mmol, 1.00 equiv.) in CH₂Cl₂ (50 mL) was thoroughly mixed with aqueous NaOH (2 M, 50 mL). The phases were separated, the combined organic layers were dried over Na₂SO₄ and evaporated under reduced pressure. The residue was dried in vacuo to afford 5c as light grey solid (0.95 g, 3.04 mmol, 97%). mp 143 – 146 °C; §H NMR (300 MHz, DMSO-d₆, δ): 7.79-7.69 (m, 8 H), 7.46 (dd, J 8.4, 1.6 Hz, 2 H), 7.42-7.36 (m, 4 H), 4.18 (s, 2 H), 2.13 (bs, 4 H); ¹³C NMR (75 MHz, DMSO-d₆, δ): 142.5, 132.7, 131.9, 127.5, 127.3, 126.9, 126.1, 125.7, 125.5, 125.2, 62.1.

1,2-Bis([4S,5S,5'S,S'S']-4,5-di(naphthalen-2-yl)-4,5-dihydro-1H-imidazol-2-yl)benzene (6c). To a solution of phthalonitrile 4 (0.18 g, 1.39 mmol, 1.0 equiv.) and N-acetyl cysteine (0.27 g, 1.67 mmol, 1.2 equiv.) in dry methanol (40 mL) at rt (argon atmosphere) was added diamine 5c (0.91 g, 2.91 mmol, 2.1 equiv.). The solution was heated to reflux for 26 h. After the reaction was cooled to rt the solution was evaporated under reduced pressure and the residue purified by silica gel chromatography (CH₂Cl₂/MeOH 50:1 + 0.1% NH₃) to give 6c as a yellow solid (0.20 g, 0.28 mmol, 20%). Rf 0.20 (CH₂Cl₂/MeOH 50:1 + 1% NH₃); mp 225-227 °C; §H NMR (500 MHz, DMSO-d₆, δ): 8.55 (bs, 2 H), 8.04-8.02 (m, 2 H), 7.83 (d, J 8.1 Hz, 4 H), 7.78 (d, J 8.5 Hz, 4 H), 7.73-7.70 (m, 10 H), 7.50 (d, J 8.5 Hz, 4 H), 7.46 (t, J 7.4 Hz, 4 H), 7.39 (t, J 7.6 Hz, 4 H), 5.01 (bs, 4 H); ¹³C NMR (126 MHz, DMSO-d₆, δ): 164.3, 141.2, 132.9, 132.4, 130.9, 130.0, 129.8, 128.3, 127.7, 127.5, 126.1, 125.8, 125.1, 54.9; MS (ESI, m/z): 719.31 [M + H⁺]; HRMS (MALDI, m/z): [M + H⁺] calcld for C₃₉H₃₉N₄, 719.31692; found, 719.31780.

(4S,4'R,5S,5'S')-2,2'-[(1,2-Phenylene)bis(4,5-di(naphthalen-2-yl)-4,5-dihydro-1H-imidazol-3-ium) chloride (7c). To a solution of bisamidine 6c (0.18 g, 0.25 mmol, 1.0 equiv.) in dry CH₂Cl₂ (25 mL) at rt (argon atmosphere) was added hydrogen chloride in Et₂O (0.27 mL, 0.54 mmol, 2.2 equiv., 2.0 M). The clear solution was stirred at rt for 2 h, evaporated under reduced pressure and dried in vacuo to obtain 7c as a yellow solid (0.20 g, 0.25 mmol, quant.). §H NMR (500 MHz, DMSO-d₆, δ): 12.10 (bs, 4 H), 8.38 (bs, 2 H), 8.18 (bs, 2 H), 7.95 (s, 4 H), 7.77-7.75 (m, 8 H), 7.63 (s, 8 H), 7.51 (td, J 7.5, 1.1 Hz, 4 H), 7.44 (t, J 7.6 Hz, 4 H), 5.63 (bs, 4 H); ¹³C NMR (126
MHZ, DMSO-d₆, δ): 164.1, 134.6, 134.1, 132.9, 132.6, 128.8, 127.8, 127.6, 127.1, 126.7, 126.5, 124.9, 123.1, 70.2.

(4S,4’S,5S,5’S)-2,2’-(1,2-Phenylene)bis(4,5-di(naphthalen-2-yl)-4,5-dihydro-1H-imidazol-3-ium) tetrais(3,5-bis(trifluoro-methyl)phenyl)borate (8c). To a solution of bisamidinium chloride 7c (0.17 g, 0.21 mmol, 1.0 equiv.) in dry methanol (24 mL) at rt (argon atmosphere) was added sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (0.37 g, 0.42 mmol, 2.0 equiv.). The clear solution was stirred at rt for 2 h and evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with brine and the aqueous phase was extracted several times with CH₂Cl₂. The combined organic phase was dried over Na₂SO₄, evaporated under reduced pressure and dried in vacuo to obtain 8c as a light yellow foam (0.46 g, 0.19 mmol, 90%). ¹H NMR (500 MHz, CD₃CN, δ): 9.53 (bs, 2 H), 8.30-8.28 (m, 2 H), 8.12 (bm, 2 H), 7.86-7.83 (m, 12 H), 7.75 (d, J 8.1 Hz, 4 H), 7.70 (bm, 16 H), 7.67 (bs, 8 H), 7.56-7.46 (m, 12 H), 5.67 (bs, 4 H); ¹³C NMR (125 MHz, CD₃CN, δ): 165.4, 162.7 (q, J₁₁b-₁₃C 49.8 Hz, BArF₄), 135.7 (BARF₄), 134.5, 134.2, 133.0, 130.4, 130.0 (q q, J₁₃C-₁₉F 31.5, 2.9 Hz, BARF₄), 129.0, 128.9, 128.2, 128.0, 127.9, 125.5 (q, J₁₃C-₁₉F 271.8 Hz, peaks at 128.8, 126.6, 124.5, 122.3, BARF₄, 125.3, 118.8 (septet, J₁₃C-₁₉F 3.8 Hz, BARF₄), 118.4, 72.1.

(1S,2S)-1,2-Di(biphenyl-4-yl)ethane-1,2-diammonium chloride (5d · 2 HCl). To a solution of ((R,R)-1,2-bis-(2-hydroxyphenyl)-1,2-diamo-no-ethane 5b (0.710 g, 2.91 mmol, 2.0 equiv.) in DMSO (15 mL) was added 4-phenylbenzaldehyde (1.21 g, 6.65 mmol, 2.40 equiv.), then stirred for 12 h at rt. Workup and imine hydrolysis were carried out as described for 5c to yield the hydrochloride of 5d as a colorless solid (1.22 g, 96%). mp 236 – 238 °C (decomp); [α]D +63 ([α]D +63 ([α]D +63 ([α]D. To a solution of bisamidine 6b (0.17 g, 0.21 mmol, 1.0 equiv.) in dry CH₂Cl₂ (25 mL) was added sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (0.89 g, 1.08 mmol, 1.0 equiv.) in dry CH₂Cl₂ (15 mL) at r (argon atmosphere) was added diamine 5d (1.54 g, 4.23 mmol, 2.2 equiv.). The solution was heated to reflux for 2 h. After the reaction was cooled to rt the solution was evaporated under reduced pressure and the residue purified by silica gel chromatography (CH₂Cl₂/MEOH 50:1 + 0.1% NH₃) to give 6d as light yellow foam (1.03 g, 1.25 mmol, 65%). Rf 0.28 (CH₂Cl₂/MEOH 25:1); ¹H NMR (300 MHz, DMSO-d₆, δ): 8.42 (bs, 2 H), 7.99-7.96 (m, 2 H), 7.70-7.67 (m, 2 H), 7.61-7.57 (m, 16 H), 7.43-7.37 (m, 16 H), 7.36-7.30 (m, 4 H), 4.83 (bs, 4 H); ¹³C NMR (125 MHz, CDCl₃, δ): 165.9, 143.5, 141.6, 141.0, 131.6, 131.3, 130.8, 129.5, 128.1, 128.0, 127.8, 127.7, 75.6; MS (ESI, m/z): 823.42 [M + H⁺]; HRMS (MALDI, m/z): [M + H⁺] calcd for C₆₀H₄₇N₄, 823.37952; found, 823.37916.

(4S,4’S,5S,5’S)-2,2’-(1,2-Phenylene)bis(4,5-di(1,1’-biphenyl)-4-yl)-4,5-dihydro-1H-imidazol-2-yl)benzene (6d). To a solution of phthalonitrile 4 (246 mg, 1.92 mmol, 1.0 equiv.) and N-acetyl cysteine (375 mg, 2.30 mmol, 1.2 equiv.) in dry methanol (40 mL) at rt (argon atmosphere) was added diamine 5d (1.54 g, 4.23 mmol, 2.2 equiv.). The solution was heated to reflux for 25 h. After the reaction was cooled to rt the solution was evaporated under reduced pressure and the residue purified by silica gel chromatography (CH₂Cl₂/MEOH 50:1 + 0.1% NH₃) to give 6d as light yellow foam (1.03 g, 1.25 mmol, 65%). Rf 0.28 (CH₂Cl₂/MEOH 25:1); ¹H NMR (300 MHz, DMSO-d₆, δ): 8.42 (bs, 2 H), 7.99-7.96 (m, 2 H), 7.70-7.67 (m, 2 H), 7.61-7.57 (m, 16 H), 7.43-7.37 (m, 16 H), 7.36-7.30 (m, 4 H), 4.83 (bs, 4 H); ¹³C NMR (125 MHz, CDCl₃, δ): 165.9, 143.5, 141.6, 141.0, 131.6, 131.3, 130.8, 129.5, 128.1, 128.0, 127.8, 127.7, 75.6; MS (ESI, m/z): 823.42 [M + H⁺]; HRMS (MALDI, m/z): [M + H⁺] calcd for C₆₀H₄₇N₄, 823.37952; found, 823.37916.

(4S,4’S,5S,5’S)-2,2’-(1,2-Phenylene)bis(4,5-di(1,1’-biphenyl)-4-yl)-4,5-dihydro-1H-imidazol-3-ium chloride (7d). To a solution of bisamidine 6d (0.89 g, 1.08 mmol, 1.0 equiv.) in dry CH₂Cl₂ (40 mL) at rt (argon atmosphere) was added hydrogen chloride solution (1.14 mL, 2.28 mmol, 2.1 equiv., 2.0 M in Et₂O). The clear solution was stirred at rt for 3 h, evaporated under reduced pressure and dried in vacuo to obtain 7d as yellow solid (0.97 g, 0.19 mmol, quant.). ¹H NMR (300 MHz, DMSO-d₆, δ): 11.95 (bs, 4 H), 8.26 (bs, 2 H), 8.13 (bs, 2 H), 7.67-7.59 (m, 24 H), 7.44-7.33 (m, 12 H), 5.55 (bs, 4 H); ¹³C NMR (125 MHz, DMSO-d₆, δ): 164.3, 140.6, 139.2, 136.1, 133.9, 132.4, 129.0, 128.4, 127.7, 127.2, 126.6, 123.0, 69.5, 54.9.
mmol, 1.0 equiv.) in dry methanol (40 mL) at rt (argon atmosphere) was added sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (1.86 g, 2.10 mmol, 2.0 equiv.). The clear solution was stirred at rt for 3 h and evaporated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$, washed with brine and the aqueous phase was extracted several times with CH$_2$Cl$_2$. The combined organic phase was dried over Na$_2$SO$_4$, evaporated under reduced pressure and dried in vacuo. After NMR-spectra showed only 1 equiv. of the BAr$_4^-$ anion, the whole procedure was repeated with 1 equiv. of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate to obtain 8d as colourless foam (2.40 g, 0.94 mmol, 90%). $^1$H NMR (500 MHz, CD$_3$CN, $\delta$): 8.17-8.15 (m, 2 H), 8.01-7.99 (m, 2 H), 7.71 (bt, 16 H), 7.67 (s, 8 H), 7.65 (s, 8 H), 7.61-7.59 (m, 8 H), 7.48 (d, J 8.3 Hz, 8 H), 7.44-7.40 (m, 8 H), 7.38-7.35 (m, 4 H), 5.32 (bs, 4 H); $^{13}$C NMR (126 MHz, CD$_3$CN, $\delta$): 165.4, 162.7 (q, J$_{13C}$-13C 49.9 Hz, BAr$_4^-$), 142.5, 140.9, 138.9, 135.7 (BAR$_4^-$), 134.7, 132.2, 130.1, 130.0 (qq, J$_{13C}$-19F 31.5, 2.9 Hz, BAr$_4^-$), 128.9, 128.8, 128.7, 127.9, 125.5 (q, J$_{13C}$-19F 272.0 Hz, peaks at 126.6, 124.5, 122.3, BarF4), 118.8 (septet, J$_{13C}$-19F 3.8 Hz, BAr$_4^-$), 118.4, 72.5 ppm.

1,2-Bis((45,55)-4,5-di(naphthalen-1-yl)-4,5-dihydro-1H-imidazol-2-yl)benzene (6e). To a solution of phthalonitrile 4 (0.11 g, 0.87 mmol, 1.0 equiv.) and N-acetyl cysteine (0.17 g, 1.04 mmol, 1.2 equiv.) in dry CH$_2$Cl$_2$ (50 mL) at rt (argon atmosphere) was added (15,25)-1,2-di(naphthalen-1-yl)ethane-1,2-diamine 5e (0.60 g, 1.92 mmol, 2.2 equiv.).$^{33}$ The solution was heated to reflux for 37 h. After the reaction was cooled to rt the solution was evaporated under reduced pressure and the residue purified by silica gel chromatography (CH$_2$Cl$_2$/MeOH 50:1 + 1% NH$_3$) to give 6e as a yellow foam (0.22 g, 0.31 mmol, 36%). R$_f$ 0.14 (CH$_2$Cl$_2$/MeOH 50:1 + 1% NH$_3$); $^1$H NMR (300 MHz, CD$_2$Cl$_2$, $\delta$): 8.01-7.98 (m, 2 H), 7.77 (bt, J 8.5 Hz, 8 H), 7.58 (dd, J 7.2, 0.9 Hz, 4 H), 7.43-7.34 (m, 10 H), 7.30 (ddd, J 8.1, 7.0, 1.0 Hz, 4 H), 6.99 (ddd, J 8.5, 7.0, 1.3 Hz, 4 H), 5.55 (bs, 4 H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$, $\delta$): 165.1, 139.9, 134.5, 131.0, 131.02, 131.0, 130.8, 129.1, 128.5, 126.2, 126.1, 126.0, 124.8, 124.0, 71.0; MS (ESI, m/z): 719.39 [M + H$^+$]; HRMS (MALDI, m/z): [M + H$^+$]+ calcd for C$_{52}$H$_{39}$N$_4$, 719.31692; found, 719.31648.

(4S,4'S,5S,5'S)-2,2'-{(1,2-Phenylene)bis(4,5-di(naphthalen-1-yl)-4,5-dihydro-1H-imidazol-3-ium) chloride (7e). To a solution of bisamidinium chloride 6e (0.19 g, 0.26 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (20 mL) at rt (argon atmosphere) was added hydrogen chloride solution (0.28 mL, 0.56 mmol, 2.2 equiv., 2.0 M in EtOH) for 3 h and evaporated under reduced pressure, the residue was dissolved in CH$_2$Cl$_2$, washed with brine and the aqueous phase was extracted several times with CH$_2$Cl$_2$. After NMR-spectra showed only 1 equiv. of the BAr$_4^-$ anion, the whole procedure was repeated with 1 equiv. of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate to obtain 8d as a yellow foam (0.56 g, 0.23 mmol, quant.). $^1$H NMR (500 MHz, CD$_3$CN, $\delta$): 8.29-8.27 (m, 2 H), 8.03 (bm, 2 H), 7.89 (d, J 8.2 Hz, 4 H), 7.86 (d, J 8.2 Hz, 4 H), 7.76 (bd, J 7.0 Hz, 4 H), 7.70 (bm, 16 H), 7.67 (bs, 8 H), 7.46 (dd, J 8.4, 7.7 Hz, 4 H), 7.34 (t, J 7.5 Hz, 4 H), 7.25 (bd, J 8.5 Hz, 4 H), 7.03 (bt, J 7.4 Hz, 4 H), 5.96 (bs, 4 H); $^{13}$C NMR (126 MHz, CD$_3$CN, $\delta$): 165.2, 162.7 (q, J$_{11B}$-$13C$ 49.8 Hz, BAr$_4^-$), 135.7 (BAr$_4^-$), 135.0, 132.4, 131.4, 130.4,
Cycloaddition of compounds 9 and 10 forming estrone precursor 13/ent-13 (Figure 5). The reaction was run in a closed 50 mL polyethylene vessel. To a solution of dienophile 10 (28.6 mg, 0.26 mmol, 1.0 equiv.) and BArF$_4$ salt 8a (117 mg, 0.052 mmol, 0.2 equiv.) in dry toluene (5 mL, argon atmosphere) at -20 °C, a spatula tip of molecular sieves (3 Å) was added. After stirring for 30 min, a solution of Dane’s diene 9 (5.4 mg, 0.29 mmol, 1.1 equiv.) in toluene (5 mL) was added to the mixture in one portion. The solution was stirred for 21 h at -20 °C and then the molecular sieves were filtered off. The solvent was removed in vacuo and the residue purified by flash column chromatography (c-hexane/EtOAc 10:1 → 4:1) to afford 13/ent-13 as light yellow foam (50.0 mg, 0.17 mmol, 65%, 28% ee, Daicel OJ, n-hexane/i-PrOH 10:4, 0.8 mL/min, 254 nm. Retention time of 13: 10.8 min (disfavored), of ent-13: 18.0 min (favored). The products were identified by comparison with authentic samples.

Base induced cycloaddition of anthrone 17 and maleimide 18 forming compound 19 (Figure 6). The reaction was run in a closed 50 mL polyethylene vessel. To a solution of anthrone 17 (42.0 mg, 0.22 mmol, 1.0 equiv.) in dry THF (6 mL) at -40 °C, the catalyst 6a (11.4 mg, 0.022 mmol, 0.1 equiv.) was added. After stirring for 30 min, maleimide 18 (38.0 mg, 0.22 mmol, 1.0 equiv.) was added to the mixture in one portion. The solution was allowed to warm up to -15 °C for 16 h and stirred for two more days at rt. The mixture was then purified by flash column chromatography (c-hexane/EtOAc 10:1) to afford product 19/ent-19 as a colourless solid (70.0 mg, 0.19 mmol, 86%, 46% ee). Single recrystallization from c-hexane/CH$_2$Cl$_2$ improved the ee to 84% (19.7 mg, 0.05 mmol, 23%, Chiralpak IA, 0.46 × 25 cm, n-hexane/i-PrOH 10:3 + 20% CH$_2$Cl$_2$, 0.7 mL/min, 254 nm. Retention time of 19: 11.6 min (favored), of ent-19: 13.2 min (disfavored). The products were identified by comparison with authentic samples.

Supplementary Material

$^1$H and $^{13}$C NMR spectra, determination of enantiomeric purities by HPLC, and crystallographic information concerning bisamidine 6a. Crystallographic data in cif format were deposited with the Cambridge Crystallographic Data Centre (deposition number 2032917) and can be obtained from the CCDC homepage (https://www.ccdc.cam.ac.uk/structures/).

References

The results described in this article originate from the PhD thesis of Dr. Mariano Goldberg: http://publikationen.ub.uni-frankfurt.de/frontdoor/index/index/docId/55098

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