A C_2-Chiral Bis(amidinium) Catalyst for a Diels–Alder Reaction Constituting the Key Step of the Quinkert–Dane Estrone Synthesis

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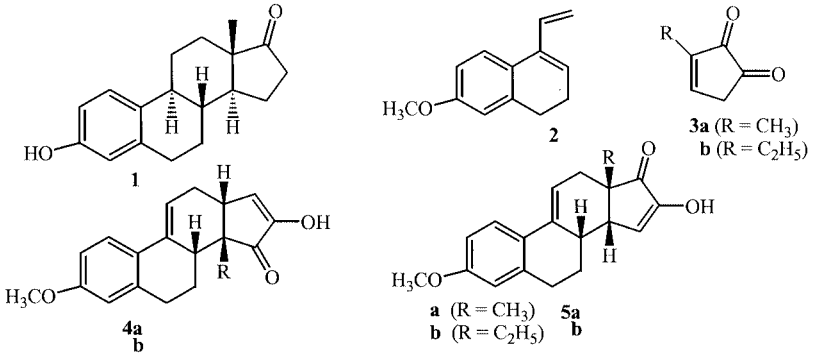
A novel C_2-chiral bis(amidinium) salt **12** has been synthesised from 5-(*tert*-butyl)isophthalic acid. The hydrogen-bond-mediated association of dienophiles **3a** and **3b** with the chiral host molecule **12** accelerates the Diels–Alder reactions with diene **2** by more than three orders of magnitude. In addition, enantioselective formation of the desired adducts is observed under catalysis with **12**. Good ratios of **4a**(**b**) + *ent*-**4a**(**b**)/**5a**(**b**) + *ent*-**5a**(**b**) from 1:10 to 1:22 were found in all reactions.

(+)-Estrone **1** and related 19-nor steroids form a prominent group of targets for organic synthesis.[1] Up to now, a considerable number of useful synthetic strategies have been proposed. Dane's early suggestion to assemble the steroidal skeleton in a Diels–Alder reaction of diene **2** and the unsaturated diketone **3a** as dienophile is certainly among them.[2] Upon closer examination, however, the reaction of **2** and **3a** turned out to produce mainly the wrong adduct, *rac*-**4a**, accompanied by small amounts of the useful intermediate *rac*-**5a** (Scheme 1).[3]

As in other cases of Diels–Alder reactions, the ratio of constitutional isomers in the cycloaddition of diene **2** and dienophiles of type **3** is sensitive to the presence of Lewis acids. Thus, it has been shown by Quinkert and co-workers that Ti^{IV} complexes may completely reverse the ratio of *rac*-**4a** and *rac*-**5a**.[4,5] Using TADDOL–Ti^{IV} complexes, enantioselectivities of adduct **5a** of up to 93% were obtained in the chirogenic cycloaddition step.[5]

A conceivable alternative strategy for promoting asymmetric Diels–Alder reactions involves the use of hydrogen bonding to position and to activate the dienophile within a chiral environment.[6] Thus, soluble amidinium salts have been shown to accelerate the cycloaddition of compounds **2** and **3a** by more than two orders of magnitude.[7]

Furthermore, the ratio of constitutional isomers is shifted in favour of adduct **5a**.[7,8] In the presence of axially chiral amidinium ions, **5a** could be obtained with considerable enantioselectivity.[8] In this case no transition metal is involved in the catalysis. This is a clear advantage for pharmaceutical intermediates with stringent restrictions on residual heavy metal content. The lengthy synthesis of axially chiral amidines[9] and the limited enantioselectivity, on the other hand, restrict the practical value of this method.



Scheme 1

An interesting class of tris(amidines) was recently introduced by Kraft.[10] Carboxylic acid salts of these com-

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pounds are characterised by hydrogen bonds between both anionic oxygen atoms and the N−H donors of two flanking amidinium groups. Based on this structural motif and the work of Buddrus,[11] we have now prepared the novel C_2-symmetric chiral bis(amidinium) salt **12** anticipating that diketones of type **3** may bind in the same way as the carboxylates in Kraft's complexes.

To warrant good substrate affinity of the catalyst by hydrogen bonding, nonpolar solvents and low temperatures are required, conditions that severely restrict the solubility of the salts. A maximum of lipophilic groups was therefore incorporated into the target structure **12**. Tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate has been shown in previous studies to reduce unwanted ion-pair interactions to a very low level.[7]

The bis(amidinium) salt **12** was prepared from 5-(*tert*-butyl)isophthalic acid (**6**) (Scheme 2). Reaction of **6** with PCl_5, followed by NH_3, afforded diamide **8**. Imidic acid ester **9** was obtained after treatment with triethyloxonium tetrafluoroborate, and could be converted into amidine **10** with (*R*,*R*)-(+)-1,2-diphenyl-1,2-ethanediamine. The route for generating catalyst **12** involves formation of picrate **11** followed by anion exchange with $Na^+[BAr'_4]^-$.

The three-dimensional structure of the picrate **11** was determined by X-ray crystallographic analysis (Figure 1).[12]

To measure the rates, yields and product ratios in the Diels−Alder reactions of **2** and **3a** or **3b**, our previously reported methods have been applied.[7,8] Solutions of diene (45 mM), dienophile (30 mM), catalyst **12** (30 mM) and 2-methoxy-6-methylnaphthalene (10 mM) as an internal standard were kept in dry CH_2Cl_2 at the temperature given in Table 1. Rates based on the disappearance of diene **2** were obtained from repeated HPLC analyses of the reaction mixture. Between one and several days was needed for complete consumption of diene **2**. After water-induced tautomerization of the initially formed diketones, the combined yield and ratio of the keto-enols (**4** + *ent*-**4**) and (**5** + *ent*-**5**) was quantified. HPLC analysis on chiral columns finally determined the enantiomeric excess.

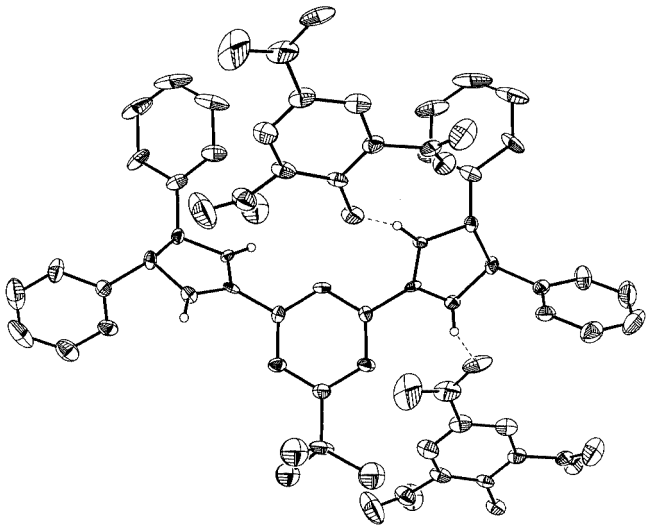
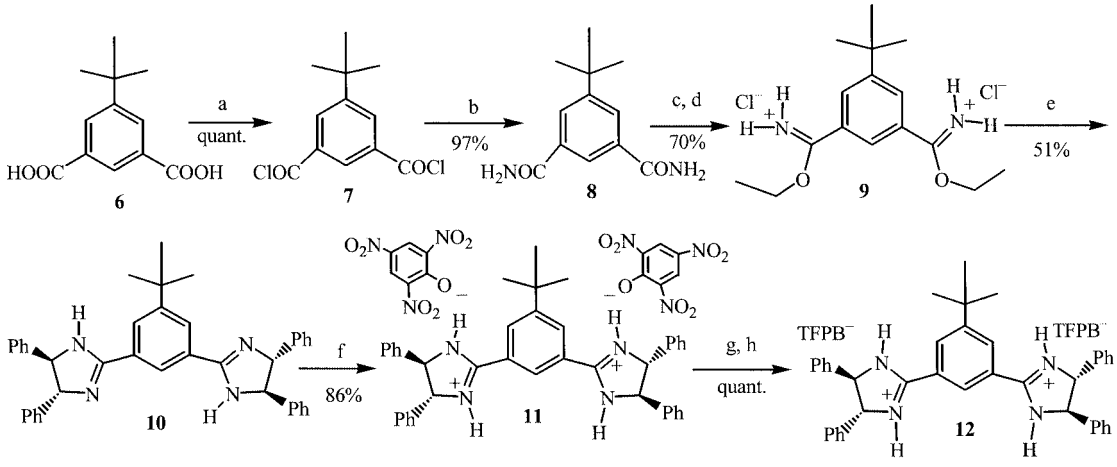


Figure 1. Molecular structure of **11**

The kinetic effects induced by the dicationic catalyst **12** surpassed by far the effects of monoamidinium salts. At +5 °C, a rate increase of more than 3000-fold was found. Good total yields and favourable ratios of constitutional isomers [**4a**(**b**) + *ent*-**4a**(**b**)]/[**5a**(**b**) + *ent*-**5a**(**b**)] of > 1:10 were seen in all reactions (Table 1).

At 5 °C, the enantioselectivity in the cycloaddition with dienophile **3a** did not reach satisfactory levels (−14%). However, the *ee* improved to −25% at −16 °C and finally reached −47% at −70 °C. At the same time, the constitutional selectivity rose from 1:10 to 1:22 with 80% total yield of cycloadducts. Catalyst **12** thus compares favourably with axially chiral amidinium salts. In the corresponding reaction with ethyl-substituted diketone **3b**, only the wrong isomer **4b** was formed with interesting stereoselectivity (−48%).

In summary, we have established a short synthetic route towards C_2-symmetric bis(amidinium) salt **12**. As a catalyst



Scheme 2. (a) PCl_5; (b) NH_3, CH_2Cl_2, room temp.; (c) Et_3OBF_4, CH_2Cl_2, room temp.; (d) HCl, EtOH, room temp.; (e) (*R*,*R*)-(+)-1,2-diphenyl-1,2-ethanediamine, EtOH, reflux; (f) picric acid, MeOH; (g) Dowex 1 × 8 Cl^- form, MeOH; (h) $NaTFPB{\cdot}2H_2O$, CH_2Cl_2/MeOH

Table 1. Diels–Alder experiments with diketones **3a** and **3b**

Dienophile	T [°C]	Yield, (%)[a]	[**4a(b)** + *ent*-**4a(b)**]/[**5a(b)** + *ent*-**5a(b)**][a]	*ee* (%)[b] **4a(b)** + *ent*-**4a(b)**	**5a(b)** + *ent*-**5a(b)**	k [$mM^{-1}·s^{-1}$][c]
3a[d] [8]	+7	<3	1:< 0.1	0	0	$<4 \times 10^{-8}$
3a	+5	80	1:13	−21	−14	1.3×10^{-4}
3a	−16	78	1:10	−40	−25	4.8×10^{-5}
3a	−70	80	1:22	−15	−47	slow
3b	−22	quant.	1:11	−48	−7	1.0×10^{-5}

[a] Yields were determined by reverse-phase HPLC (Merck Purospher 100 RP-18). [b] All enantiomeric excesses were determined by HPLC on a chiral phase column (Daicel OJ-R 150 × 4 mm). A negative *ee* stands for an excess of *ent*-**5a** or *ent*-**5b** (slower running enantiomer); in the case of **4a(b)** and *ent*-**4a(b)** it means an excess of the enantiomer with the longer retention time (the absolute configuration has not been determined experimentally). [c] Second-order rate constants are based on the decrease of the diene concentration. Since glass surfaces influence rates and product distributions, all reactions were run in polyethylene vials. [d] The reaction was carried out in the absence of catalyst **12**.

in a Diels–Alder reaction forming the skeleton of estrone and norgestrel, **12** is clearly superior to axially chiral monoamidinium salts as far as rates and constitutional selectivity are concerned.

Although the enantioselectivities achieved are still too low to be of practical use, substituting the phenyl group in the diamino building block by sterically more demanding groups is a promising strategy for future optimisation.

Experimental Section

General: Solvents were distilled before use: CH_2Cl_2 (P_4O_{10}), EtOH (Na), MeCN (CaH_2). HPLC column: Merck LiChrospher 100 RP-18 (5 μm), 125 × 4 mm; Daicel OJ-R, 150 × 4 mm. Melting points (uncorrected): hot plate microscope. ^{1}H NMR spectra were recorded at 250 and 400 MHz; chemical shifts (δ) are given in ppm, and J in Hz.

5-*tert*-Butyl-1,3-benzenedicarboxamide (8): Compound **6** (2.5 g, 11.25 mmol, 1 equiv.) was mixed with PCl_5 (7 g 33.74 mmol; 3 equiv.) and heated until a slightly yellow liquid containing **7** was formed. This was added dropwise to vigorously stirred CH_2Cl_2 (350 mL), saturated with NH_3. The reaction mixture was stirred at room temp. overnight. The precipitate was filtered, washed with water and dried. Recrystallisation from methanol gave 2.39 g (97%) of amide **8** as colourless crystals, m.p. 246–248 °C. ^{1}H NMR (250 MHz, DMSO): δ = 8.19 (t, J = 1.5 Hz, 1 H), 8.03 (s, 2 NH), 8.00 (d, J = 1.5 Hz, 2 H), 7.38 (s, 2NH), 1.32 (s, 9 H) ppm. $C_{12}H_{16}N_2O_2$ (220.27): calcd. C 65.43, H 7.32, N 12.72; found C 65.66, H 7.35, N 12.76.

Diethyl 5-*tert*-Butyl-1,3-benzenedicarboximidate, Salt with Hydrochloric Acid (9): A mixture of amide **8** (500 mg, 2.26 mmol), triethyloxonium tetrafluoroborate (1.24 g, 6.52 mmol) and dry CH_2Cl_2 (4 mL) was stirred at room temp. under argon for 20 h. To the resulting precipitate was added 40 mL of CH_2Cl_2 and 50 mL of sat. aq. $NaHCO_3$. The organic phase was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure. Flash chromatography (silica gel; hexane/EtOAc, 1:2) gave the imidic acid ester as a colourless oil (440 mg, 70%). IR (NaCl, film): $\tilde{\nu}$ = 3418, 3173, 2962, 2606, 2345, 1718, 1702, 1677, 1654, 1624, 1589, 1560, 1438, 1399, 1364, 1295, 1248, 1164, 1028 cm^{-1}. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 9.00 (s, 2NH), 8.06 (m, 1 H), 7.95 (d, J = 1.5 Hz, 2 H), 4.25 (q, J = 7.1 Hz, 4 H), 1.32 (t, J = 7.1 Hz, 6 H), 1.31 (s, 9 H) ppm. A solution of the imidic acid ester (440 mg, 1.59 mmol) in 25 mL of EtOH was treated with 3 mL of 1 N HCl and stirred for 10 min at room temperature. Removal of the solvent in vacuo afforded 550 mg (quant.) of hydrochloride **9** as a colourless solid, m.p. 174–175 °C. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 8.32 (s, 1 H), 8.20 (s, 2 H), 7.07–7.48 (m, $NH_2^+Cl^-$), 4.35 (q, J = 7.1 Hz, 4 H), 1.36 (s and t, 15 H, J = 7.1 Hz) ppm. $C_{16}H_{26}Cl_2N_2O_2$ (349.3): calcd. C 55.02, H 7.50, N 8.02; found C 54.93, H 7.39, N 8.19.

Imidazole 10: A solution of (+)-(1*R*,2*R*)-diphenylethylenediamine (226.9 mg, 1.069 mmol) and hydrochloride **9** (186 mg, 0.536 mmol) in anhydrous EtOH (2.8 mL) was stirred for 1 h at room temp. and for 4 h at reflux. After evaporation of the solvent at reduced pressure, the residue was dissolved in CH_2Cl_2 (27 mL) and the solution was extracted with 5% aq Na_2CO_3 (25 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure. Further purification by flash chromatography (EtOAc/hexane, 10:1) gave **10** (158 mg, 51%) as a colourless solid, m.p. 135–140 °C. IR (NaCl, film): $\tilde{\nu}$ = 3375, 3168, 3061, 3028, 2963, 2868, 2369, 1947, 1870, 1802, 1718, 1670, 1623, 1576, 1492, 1452, 1419, 1364, 1275, 1204, 1154, 1028, 1009, 894, 851, 758 cm^{-1}. ^{1}H NMR ([D_6]DMSO): δ = 8.55 (s, 1 H), 8.15 (s, 2 H), 8.00 (s, 2 NH), 7.3 (m, 20 H), 4.95 (d, 2 H), 4.70 (d, 2 H), 1.35 (s, 9 H) ppm. ESI-MS: m/z = 575.5 $[M + H]^+$.

Bis(amidinium) Picrate 11: A solution of 183 mg of 40% picric acid (0.48 mmol, 2 equiv.) in 1.5 mL of methanol was added to a solution of **10** (140 mg, 0.24 mmol, 1 equiv.) in 1 mL of methanol. The addition of 0.5 mL of water led to the formation of a yellow precipitate. Crystals of **11** suitable for X-ray structure analysis were grown from acetone and diethyl ether by slow evaporation of the solvent at +5 °C; m.p. 162–164 °C (m.p. 145–149 °C from MeOH and H_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1 H), 8.61 (s, 2 H), 8.45 (s, 4 H), 7.11–7.26 (m, $20H_{arom}$), 5.16 (s, 4 H), 1.29 (s, 9 H) ppm. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.58 (s, 4 H), 8.57 (s, 1 H), 8.50 (s, 2 H), 7.50 (m, 20 H), 5.46 (s, 4 H), 1.42 (s, 9 H) ppm. $C_{52}H_{46}N_{10}O_{15}$ (1050.98) (**11**·H_2O; from MeOH and H_2O): calcd. C 59.43, H 4.41, N 13.33; found C 59.31, H 4.67, N 13.39. The single-crystal structure of the bis(amidinium) picrate (**11**·Et_2O) was determined at 173 K with a Siemens-SMART-CCD three-circle diffractometer. The structure was solved by direct methods. CCDC-192449 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. The single-crystal structure of a related

chloroform solvate (**11**·2$CHCl_3$) was also determined (CCDC-192448).

Bis(amidinium) Tetrakis(aryl)borate 12: Picrate **11** (98 mg, 0.095 mmol) was dissolved in 10 mL of methanol and filtered through Dowex 1 × 8 Cl^- form (200−400 mesh). The solvent was removed in vacuo. The corresponding residue was dissolved in CH_2Cl_2 (3 mL) and treated with a solution of tetrakis(3,5-bistrifluoromethylphenyl)borate (NaTFPB·2H_2O; 190.5 mg, 0.206 mmol; 2.1 equiv.) in 5 mL of MeOH. After stirring the clear solution at room temperature for 30 min, the solvent was removed in vacuo and the residue treated with CH_2Cl_2. The suspension was washed twice with H_2O and the organic layer dried with Na_2SO_4. Removal of the solvent in vacuo afforded 217.5 mg (99.5%) of **12** as a colourless solid with m.p. 45−48 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 8.62 (s, 1 H), 8.50 (s, 2 H), 7.75 (s, 8 H), 7.63 (s, 16 H), 7.50 (m, 20 H), 5.45 (s, 4 H), 1.42 (s, 9 H) ppm. $C_{104}H_{64}B_2F_{48}N_4$ (2303.19): calcd. C 54.23, H 2.80, N 2.43; found C 54.24, H 2.96, N 2.50.

Acknowledgments

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[12] Crystal data for (**11**·Et_2O): $C_{56}H_{54}N_{10}O_{15}$, M = 1107.09, monoclinic, space group C_2, a = 17.9670(10), b = 13.3150(10), c = 13.7960(10) Å, β = 122.910(10)°, V = 2770.8(3) $Å^3$, Z = 2, D_x = 1.327 $Mg·m^{-3}$, Mo-K_α radiation, λ = 0.71073 Å, Cell parameters from 4887 reflections, θ = 1.76−25.03°, μ = 0.098 mm^{-1}, T = 173 (2) K, crystal size 0.58 × 0.32 × 0.12 mm.

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