Catalysis of a Diels−Alder Reaction by Amidinium Ions

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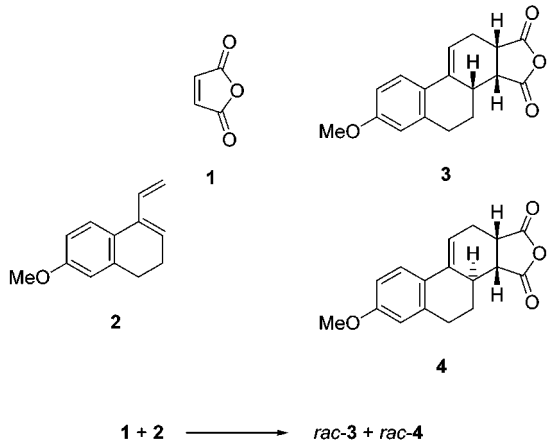
Amidines and guanidines are important functional groups in molecular recognition and host−guest chemistry. Here it is shown that lipophilic amidinium ions catalyze a cycloaddition reaction representing the key step of the Quinkert−Dane estrone synthesis. Hydrogen-bond-mediated association with the organic cation leads to an electrophilic activation of the dienophile and to enhanced rates of the Diels−Alder reaction. The observed effects are similar to those expected from mild Lewis acids. In competition experiments, amidinium catalysis favors the reaction of the less electron deficient dienophile.

Introduction

Among synthetic receptor molecules based on amidinium and guanidinium ions, good catalysts for phosphoryl transfer reactions can be found.[1,2] Their mode of action is to increase substrate electrophilicity by forming hydrogen bonded ion pairs. It has been shown earlier that organic cations may also associate with neutral carbonyl compounds.[3] The enhanced guest electrophilicity in those complexes should accelerate reactions with nucleophiles and cycloadditions.[4] Lewis acids are common catalysts for Diels−Alder reactions. In lithium perchlorate promoted cycloadditions, again the Lewis acidity of the cation is exploited.[5] In rare cases, even weaker electrophiles are sufficient for catalysis: Diels−Alder reactions have been accelerated by complexing dienophiles to hydrogen-bond-forming receptors.[6] Since amidinium ions are good hydrogen bond donors, they might catalyze cycloadditions in a similar way. In contrast to lithium perchlorate, the shape of amidinium salts can be easily optimized for certain applications, e.g. by introduction of chirality.[7] Here we present two examples of amidinium-catalyzed [4 + 2] cycloadditions. The first reaction constitutes a simple case in which *rac*-**3** is formed from maleic anhydride **1** and diene **2** (Scheme 1).[8] A more complex behavior is observed in the cycloaddition of **2** and diketone **5**.[9] This reaction leads to *rac*-**8**, a key intermediate in the Quinkert−Dane synthesis of estrone (Scheme 2).[10]

Scheme 1



Results and Discussion

To favor the association of amidinium groups and dienophiles, less polar solvents and noncoordinating counterions are essential. Structure **12** was chosen instead of simpler amidines to guarantee sufficient solubility of the salts (Scheme 3). Starting from palmitoyl amide **10**,[11] we prepared the amidinium tetrafluoroborate **12a** via O-alkylation (**11**; 86%) and ammonolysis (46%). Anion exchange then produced the tetraaryl borate salts **12b**−**d**.[12] While all three compounds are soluble in CH_2Cl_2, a strong tendency for ion pairing was seen in **12b**. The ^{1}H NMR signal of the a methylene group (δ = 2.33

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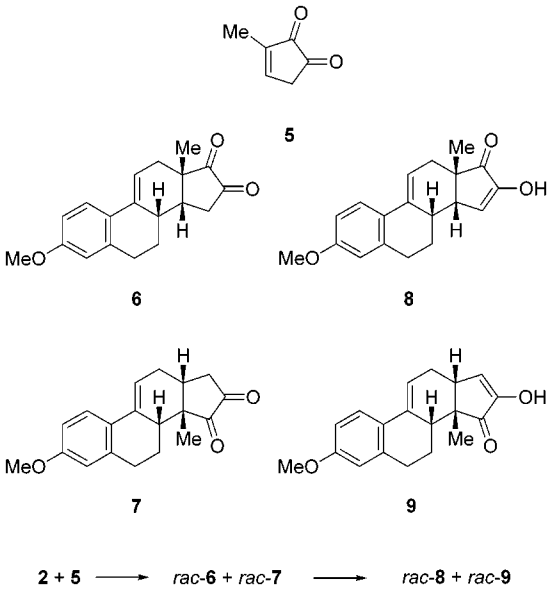
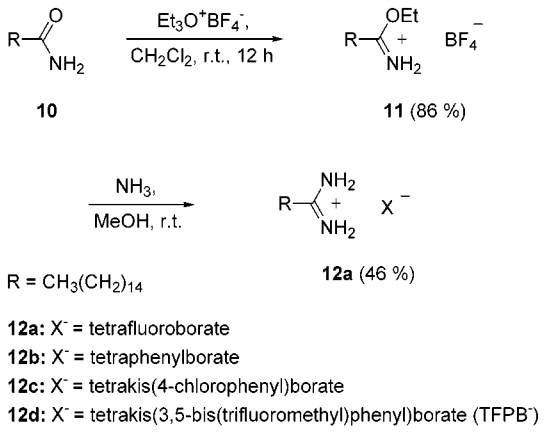
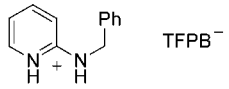
Scheme 2



Scheme 3





in DMSO-d_6) is shifted to 0.95 ppm in $CDCl_3$. We attribute this shift to a ring current effect from a tightly bound tetraphenyl borate ion. In compound **12c** the effect was reduced (δ = 1.43) and completely absent in compound **12d** (δ = 2.33, $CDCl_3$). All kinetical studies, therefore, used the latter salt.[13] The 2-(benzylamino)-pyridinium salt **13** may be seen as a heterocyclic analogue of an amidinium ion.[14] Compared to **12a**−**d**, its acidity is distinctly increased.

The reaction of maleic anhydride **1** with diene **2** (CH_2Cl_2, 7 °C, 24 h) produced 75% of *rac*-**3** together with 13% of the exo isomer *rac*-**4** (Scheme 1).[15] Reaction rates and yields were determined by HPLC using 2-methoxy-6-methylnaphthalene (**14**) as internal standard (k_2 = 2.5 × 10^{-6} mM^{-1} s^{-1}).[16] In ^{1}H NMR titrations with amidinium salt **12d** ($CDCl_3$, 7 °C), a low-field shift of the NH signals was seen upon addition of maleic anhydride. However, the association must be weak since the shift remained small and could not be saturated. Electron-poor anhydrides have been shown previously to possess the lowest affinities toward organic cations within a series of carbonyl compounds.[3] In consequence, the amidinium salts **12d** and **13** did not induce large rate effects (Table 1). The ratio of the endo and exo isomers *rac*-**3**:*rac*-**4** was shifted in favor of endo.

Table 1. Diels−Alder Experiments with Maleic Anhydride 1

catalyst (no. of equiv)	ratio[a] *rac*-**3**:*rac*-**4**	acceleration	yield[a] after 4 h (%)
no catalyst	6:1	1	63[b]
12d (1)	14:1	2.5	82
13 (0.5)	11:1	1.7	74
13 (1)	13:1	2.6	82
13 (2)	17:1	3.9	88

[a] The yields and ratios were determined by HPLC. [b] 88% yield after 24 h.

Enolization of diketone **5** would form a cyclopentadienone derivative with antiaromatic properties. As a result, **5** prefers the keto form, a rare exception within the class of 1,2-dicarbonyl compounds. In contrast to maleic anhydride, diketone **5** readily associates with amidinium salt **12d**. K_a could be determined by ^{1}H NMR titration (37 ± 6 M^{-1}; $CDCl_3$, 7 °C). The stability constant for the complex **13**·**5** was estimated in the same way (70 ± 20 M^{-1}; $CDCl_3$, 7 °C). Further evidence for association came from the mass spectra of **13** when 100 equiv of diketone **5** was added. In the presence of an equimolar mixture of maleic anhydride and diketone, only the complex **13**·**5** could be detected. Accordingly, ESI-MS permits to select good binding partners within a mixture or small library of weakly coordinating guest molecules.

The Diels−Alder reaction of diene **2** and diketone **5** (Scheme 2) is complicated by the existence of constitutional isomers and by the slow tautomerization to the final keto enols. In addition, special care is necessary to avoid artifacts: glass surfaces and silica gel are good catalysts and influence both rates and product ratios.[17] All reactions therefore were run in polyethylene vials (CH_2Cl_2, 7 °C). Analytical samples, quenched in acetonitrile and stored in liquid nitrogen, proved to be sufficiently stable. They were analyzed without further workup by HPLC, again using naphthalene **14** as internal standard. Pure samples of diene **2**, **14**, product *rac*-**8**, and isomeric product *rac*-**9** were prepared according to published procedures and applied to the calibration of the HPLC system. In the absence of catalysts, the reaction produced *rac*-**8** and *rac*-**9** (ratio < 0.1:1) slowly and in low yield (<3%). Under these conditions, most of the diene **2** decomposed. Good total yields and ratios of *rac*-**8** and *rac*-**9** around 3:1 were found in all amidinium-promoted reactions (Table 2). Covalent adducts of amidines and diketones, which might have formed under basic conditions, could not be detected. Interestingly, when the

(13) In our initial experiments, isolated yields of *rac*-**8** and *rac*-**9** were determined instead of reaction rates. In accordance with their tendency of ion pairing, **12b** led to the lowest and **12d** to the best yields. The tetrafluoroborate salt **12a** was not sufficiently soluble to be tested.

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Table 2. Diels−Alder Experiments with Diketone 5

catalyst (no. of equiv)	ratio[a] *rac*-**8**:*rac*-**9**	acceleration	yield[a] after 7 d[b] (%)
no catalyst	<0.1:1	1	<3
12d (1)	2.6:1	100	82[c]
13 (0.25)	3.5:1	125	93
13 (0.5)	3.3:1	300	∼100
13 (1)	3.3:1	450	∼100

[a] The yields and ratios were determined by HPLC. [b] The long times are due to the slow tautomerization of *rac*-**6** and not to the Diels−Alder reaction. [c] The tautomerization was enforced by addition of H_2O in MeCN (7 d, room temperature). Otherwise it was incomplete even after 14 d.

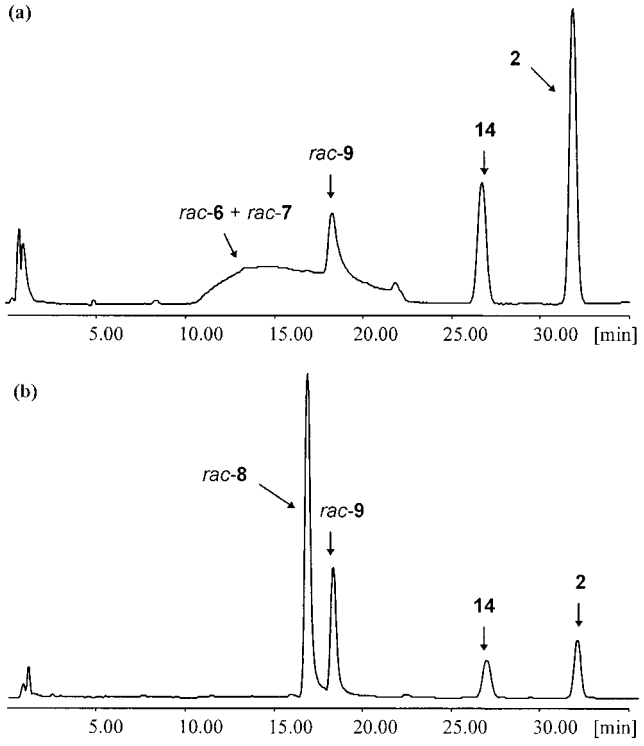

Figure 1. Diels−Alder reaction of diene **2** with diketone **5**: Typical chromatograms of the reaction mixture before (a) and after (b) tautomerization of *rac*-**6** and *rac*-**7**.

reactions were analyzed after a short time, HPLC suggested high selectivities in favor of *rac*-**9**. At the same time, broad and intense peaks were present which later disappeared (Figure 1). Simultaneous analysis of reaction kinetics by HPLC, infrared, and UV−vis spectroscopy gave good evidence that this effect is caused by the initial cycloadducts, the electrophilic 1,2-diketones *rac*-**6** and *rac*-**7**. The water content of the HPLC solvent allows formation of carbonyl hydrates during separation thus causing peak broadening.[18] While *rac*-**7** rapidly tautomerizes producing *rac*-**9**, the corresponding reaction of *rac*-**6** is slow. Reaction rates, therefore, had to be calculated on the disappearance of diene **2**. Good rate enhancements were seen in all cases (Table 2). The heterocyclic compound **13** turned out to be distinctly more efficient than palmitamidinium salt **12d**. In the presence of 1 equiv of **13**, a 450-fold rate increase was observed. Substoichiometric amounts of catalyst led to proportionally reduced rates, but the yield and product distribution remained constant.

In uncatalyzed competition experiments of diene **2** with both dienophiles **1** and **5**, only the cycloadducts of maleic anhydride were formed (*rac*-**3**:*rac*-**4** = 6:1). Since compound **13** quite selectively accelerates the reaction of diketone **5**, the catalyst might switch the product distribution. As expected, in the presence of **13** the estrone precursor *rac*-**8** became the main constituent of the mixture (total yield determined by HPLC: 83%; *rac*-**8**:*rac*-**9**:*rac*-**3**:*rac*-**4** = 19:6:12:1).

The results have demonstrated that amidinium ions can accelerate Diels−Alder reactions with considerable substrate selectivity. The endo adducts are favored, and product distributions are shifted in a way typical for Lewis acid-catalyzed processes. A first report on the catalysis of Diels−Alder reactions by axially chiral amidinium ions has been published recently.[19,20]

Experimental Section

Methylene chloride was filtered over alumina B, activity I before use. HPLC column: Merck LiChrospher 100 RP-18 (5 mm), 125 × 4 mm. Mp: hot plate microscope, uncorrected. ^{1}H NMR spectra were recorded at 200, 250, 270, and 400 MHz; chemical shifts (δ) are given in ppm, and J in Hz. The diene **2**,[10] the diketone **5**,[9] and the reference substances *rac*-**8** and *rac*-**9**[10] were prepared according to published methods.

(±)-3-Methoxy-16-oxa-14β-gona-1,3,5(10),9-tetraen-15,17-dione (*rac*-3) and (±)-3-Methoxy-16-oxa-8α,14β-gona-1,3,5(10),9-tetraen-15,17-dione (*rac*-4). These were prepared by a slight modification of Andreev's method:[15] Diene **2** (400 mg, 2.15 mmol) and maleic anhydride **1** (211 mg, 2.15 mmol) were dissolved in 20 mL of CH_2Cl_2 and stirred overnight at room temperature. After removal of the solvent in vacuo, crystallization of the residue from Et_2O/*n*-hexane afforded 410 mg (67%) of *rac*-**3** as colorless needles. Purification of the mother liquid by semipreparative HPLC (10:2 *n*-hexane/EtOAc + 30% CH_2Cl_2, MN Nucleosil 50-10, 250 × 10 mm, 10 mL/min, 254 nm) afforded a further 24 mg (4%; 71% combined overall yield) of *rac*-**3** and after recrystallization from Et_2O/*n*-hexane 20 mg (3%) of *rac*-**4** as yellowish needles.

(±)-3-Methoxy-16-oxa-14β-gona-1,3,5(10),9-tetraen-15,17-dione (*rac*-3): mp 205−206 °C (lit.:[8b] mp 203−204 °C); ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1, J = 8.9), 6.73 (dd, 1, J = 8.6, 2.4), 6.64 (d, 1, J = 2.7), 6.24−6.27 (m, 1), 3.44−3.54 (m, 2), 3.79 (s, 3), 2.91−2.97 (m, 1 H), 2.76−2.81 (m, 1), 2.76−2.81 (m, 1), 2.60−2.73 (m, 2), 2.32−2.39 (m, 1), 2.21−2.31 (m, 1), 2.08−2.15 (m, 1); IR (KBr) 3080, 2996, 2954, 2940, 2923, 2843, 1841, 1771, 1607, 1494. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.94; H, 5.80.

(±)-3-Methoxy-16-oxa-8α,14β-gona-1,3,5(10),9-tetraen-15,17-dione (*rac*-4): mp 189−191 °C (lit.:[15] mp 189.5−191 °C); ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1, J = 8.7), 6.76 (dd, 1, J = 8.7, 2.7), 6.66 (d, 1, J = 2.7), 6.35−6.40 (m, 1), 3.81 (s, 3), 3.24 (td, 1, J = 9.9, 7.9), 2.84−2.97 (m, 2), 2.73−2.78 (m, 2), 2.46−2.61 (m, 2), 2.27−2.39 (m, 1), 1.60−1.76 (m, 1). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.58; H, 5.82.

1-Ethoxy-1-hexadecanimine, Tetrafluoroborate Salt (11). A suspension of palmitoyl amide **10**[11] (25 g, 99 mmol) in 300 mL of dry CH_2Cl_2 was cooled to 0 °C, treated with a solution of triethyloxonium tetrafluoroborate (26 g, 136 mmol) in dry CH_2Cl_2 (50 mL), and stirred overnight at room temperature. After filtration over Celite, the solution was concentrated in vacuo to a volume of 100 mL. Addition of 400 mL of Et_2O afforded 31 g (86%) of **11** as colorless crystals: mp 67−

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(20) The observation of significant enantioselectivities gives further evidence that amidinium catalysis is due to complex formation of cation and dienophile. Chirality transfer from amidinium ions to cycloadduct **8** cannot be explained by simple acid catalysis.

70 °C; ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1), 8.85 (s, 1), 4.49 (q, 2, J = 7.0), 2.66 (t, 2, J = 7.7), 1.64−1.73 (m, 2), 1.51 (t, 3, J = 7.0), 1.19−1.31 (m, 24), 0.88 (t, 3, J = 6.8). Anal. Calcd for $C_{18}H_{38}BF_4NO$: C, 58.23; H, 10.32; N, 3.77. Found: C, 58.01; H, 10.12; N, 3.90.

Hexadecanamidine, Tetrafluoroborate Salt (12a). 11 (9.46 g, 25 mmol) was dissolved in 100 mL of a saturated ammonia solution in MeOH and stirred overnight at room temperature. After filtration over Celite, the solvent was removed in vacuo. Recrystallization of the residue from 1:2 dioxane/Et_2O afforded 3.97 g (46%) of **12a** as colorless crystals: mp 108 °C; ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 2), 8.31 (s, 2), 2.34 (t, 2, J = 7.7), 1.59 (m, 2), 1.16−1.24 (m, 24), 0.86 (t, 3, J = 6.5). Anal. Calcd for $C_{16}H_{35}BF_4N_2$: C, 56.15; H, 10.31; N, 8.18. Found: C, 55.92; H, 10.37; N, 8.08.

Hexadecanamidine, Salt with Tetraphenylborate (12b). A solution of **12a** (2.60 g, 7.58 mmol) in 60 mL of MeOH was treated with sodium tetraphenylborate (2.90 g, 8.47 mmol) dissolved in 60 mL of MeOH. Addition of water precipitated 3.83 g (87%) of **12b** as colorless crystals: mp 119 °C; ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 2), 8.36 (s, 2), 7.18 (m, 8), 6.93 (m, 8), 6.78 (m, 4), 2.33 (t, 2, J = 7.7), 1.55−1.61 (m, 2), 1.20−1.28 (m, 24), 0.85 (t, 3, J = 6.5); ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 8), 7.03 (yt, 8), 6.83 (t, 4, J = 7.2), 3.03 (s, 4), 1.11−1.31 (m, 24), 0.95 (t, 2, J = 7.7), 0.88 (t, 3, J = 6.8), 0.72 (m, 2). Anal. Calcd for $C_{40}H_{55}BN_2$: C, 83.60; H, 9.65; N, 4.87. Found: C, 83.36; H, 9.65; N, 5.15.

Hexadecanamidine, Salt with Tetrakis(4-chlorophenyl)borate (12c). A solution of **12a** (0.69 g, 2.02 mmol) and potassium tetrakis(4-chlorophenyl)borate (1.05 g, 2.12 mmol) in 30 mL of 1:1 MeOH/H_2O was treated with 30 mL of CH_2Cl_2 and stirred for 30 min. The organic layer was separated, the aqueous layer was extracted with an additional portion of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. Removal of the solvent in vacuo afforded 1.39 g (97%) of **12c** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.39−7.43 (m, 8), 7.04 (d, 8, J = 8.2), 3.74 (s, 4), 1.43 (t, 2, J = 7.4) 1.00−1.31 (m, 26), 0.88 (t, 3, J = 6.6). Anal. Calcd for $C_{40}H_{51}BCl_4N_2$: C, 67.43; H, 7.22; N, 3.93. Found: C, 67.36; H, 7.17; N, 3.81.

Hexadecanamidine, Salt with Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (12d). A suspension of **12a** (171 mg, 0.5 mmol) in 5 mL of MeOH was treated with a solution of NaTFPB·$2H_2O$[12] (461 mg, 0.5 mmol) in 5 mL of MeOH. After stirring the clear solution for 10 min at room temperature, 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 over Na_2SO_4. Removal of the solvent in vacuo afforded 553 mg (99%) of **12d** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 8), 7.55 (s, 4), 7.36 (s, 2), 6.43 (s, 2), 2.33 (t, 2, J = 8.0), 1.52−1.60 (m, 2), 1.22−1.29 (m, 24), 0.87 (t, 3, J = 6.8). Anal. Calcd for $C_{48}H_{47}BF_{24}N_2$: C, 51.54; H, 4.23; N, 2.50. Found: C, 51.44; H, 4.52; N, 2.28.

2-(Benzylamino)pyridinium Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (13). A solution of 2-(benzylamino)-pyridine[14] (92 mg, 0.5 mmol) in 10 mL of EtOH was treated with 0.6 mL of 1 N HCl and stirred for 10 min at room temperature. The solvent was removed in vacuo. The residue was redissolved in 10 mL of EtOH and a solution of NaTFPB·$2H_2O$[12] (461 mg, 0.5 mmol) in 5 mL of EtOH was added. After removal of the solvent in vacuo, the residue was taken up in CH_2Cl_2 and washed twice with water. Drying of the organic layer over $MgSO_4$ and removal of the solvent in vacuo afforded 496 mg (94%) of **13** as a colorless solid: mp 78−84 °C; ^{1}H NMR (DMSO-d_6) δ 13.29 (s, 1), 8.86 (s, 1), 7.93 (d, 1, J = 6.1), 7.83 (t, 1, J = 7.3), 7.70 (s, 4), 7.60 (s, 8), 7.29−7.40 (m, 5), 7.04 (d, 1, J = 8.8), 6.85 (t, J = 6.6), 4.55 (d, 2, J = 5.3). Anal. Calcd for $C_{44}H_{25}BF_{24}N_2$: C, 50.40; H, 2.40; N, 2.67. Found: C, 50.56; H, 2.70; N, 2.63.

Calibration of the HPLC System. A 4 μmol amount of **2**, *rac*-**3**, *rac*-**4**, *rac*-**8**, or *rac*-**9** was dissolved in 10 mL of a 1.5 mM solution of **14**.[16] These solutions were analyzed by HPLC: injection volume, 20 μL; solvent, MeCN/H_2O; linear gradient from 30 to 50% MeCN in 20 min, then 5 min of 50% MeCN, and finally from 50 to 70% MeCN in 15 min; flow rate 1 mL min^{-1}; UV detection at 260 nm. Calibration factors (cf) for each compound were obtained from the UV integrals: cf = area(**14**)[compound]/area(compound)[**14**]: **2**, cf = 0.85 (t_R = 32.6 min); *rac*-**3**, cf = 0.27 (t_R = 19.1 min); *rac*-**4**, cf = 0.27 (t_R = 21.9 min); *rac*-**8**, cf = 0.22 (t_R = 18.1 min); *rac*-**9**, cf = 0.23 (t_R = 19.4 min); **14**, cf = 1.00 (t_R = 28.4 min). The concentration of each compound was then calculated: [compound] = area(compound)[**14**]cf/area(**14**).

General Procedure for the Diels−Alder Experiments. Into a 1.5-mL polyethylene vial (Eppendorf tube) containing catalysts **12d** or **13** (0, 0.25, 0.5, 1, or 2 equiv) were added 250 μL of a 60 mM CH_2Cl_2 solution of dienophiles **1** or **5** and 250 μL of a 90 mM solution of the diene **2** in CH_2Cl_2 containing 5 μmol of the standard **14**. The final concentrations at t = 0 were 30 mM of dienophile, 45 mM of diene, 10 mM of 14, and 0, 7.5, 15, 30, or 60 mM of the catalyst. The reaction mixture was stored at 7−8 °C in a cold room for 14 d. Aliquots (10 μL) were taken after 1, 5, 15, 30, 60, 120, and 240 min and 1, 2, 4, 7, and 14 d, diluted with 500 μL of MeCN, and stored at −196 °C. The samples were analyzed by HPLC under the conditions given above. The second-order rate constants k_2 were obtained by fitting the concentrations of diene **2** to the experimental values of the first 4 h (variables: k_2 and k_{decomp}; $d[\mathbf{2}] = -k_2[\mathbf{2}][\text{dienophile}]dt - k_{decomp}[\mathbf{2}]^2dt$). The concentration of **2** decreased independently from the Diels−Alder reaction by decomposition. This minor effect could be empirically described by the correction term $k_{decomp}[\mathbf{2}]^2dt$. In the noncatalyzed reaction of **2** and **5**, an upper limit of $k_2 = 4 \times 10^{-8}$ mM^{-1} s^{-1} could be estimated. Rate accelerations shown in Table 2 are based on this number.

Simultaneous Analysis of the Diels−Alder Reaction by HPLC, UV, and IR. Into a 3-mL vial containing catalyst **13** (62.91 mg, 60 μmol) were added 1 mL of a 60 mM CH_2Cl_2 solution of **5** and 1 mL of a 90 mM solution of the diene **2** in CH_2Cl_2 containing 20 μmol of the standard **14**. The final concentrations at t = 0 were 30 mM of dienophile, 45 mM of diene, 10 mM of **14**, and 30 mM of **13**. A 500 μL volume was transferred into a 1 mm UV quartz cell and stored at 7 °C. The rest of the reaction mixture was also stored at 7 °C and used for IR and HPLC analysis. IR and UV spectra were measured without further manipulation. Aliquots (10 μL) for HPLC analysis were diluted with 500 μL of MeCN and analyzed under the conditions given above. UV and IR spectra and HPLC analyses were done after 15, 60, and 240 min and 2, 7, 14, and 21 d. Within 4 h, a broad band around 400 nm developed in the UV spectra. In the IR spectra, the initial diketone signals (1720, 1774 cm^{-1}) were replaced by a signal at 1747 cm^{-1}. At the same time a broad peak appeared in the HPLC chromatograms. When the concentration of *rac*-**8** increased in the HPLC chromatogram, these signals (UV, IR, HPLC) bled and completely disappeared after 21 d. The coincidence of the phenomena in all three analytical methods gave strong evidence that the same intermediates are responsible for each of the effects: the diketones *rac*-**6** and *rac*-**7**.

Competition Experiment. Into a 1.5-mL polyethylene vial containing catalyst **13** (14.15 mg, 13.5 μmol) were added 150 μL of a 90 mM CH_2Cl_2 solution of **1**, 150 μL of a 90 mM CH_2Cl_2 solution of **5**, and 150 μL of a 72 mM solution of the diene **2** in CH_2Cl_2 containing 4.5 μmol of the standard **14**. The final concentrations at t = 0 were 30 mM of each dienophile, 24 mM of diene, 10 mM of **14**, and 30 mM of catalyst **13**. The reaction mixture was stored at 7−8 °C for 4 h. Samples were taken after 1, 60, 120, 180, and 240 min and analyzed as described above to determine the yields of *rac*-**3** and *rac*-**4**. After 3 h, diene **2** was no longer detectable. To prevent an acylation of the keto enols *rac*-**8** and *rac*-**9** by the anhydrides, an identical sample was quenched with 500 μL of water. After 4 d at room temperature, the tautomerization of *rac*-**6** and *rac*-**7** was complete and allowed one to determine the yields of *rac*-**8** and *rac*-**9**. Compounds *rac*-**3** and *rac*-**4** were hydrolyzed by this procedure.

General Procedure for the ^{1}H NMR Titration. Into eight different NMR tubes containing 200 μL of a 60 mM solution of catalyst **12d** or **13** in $CDCl_3$ were added 0, 5, 10, 20, 40, 80, 160, or 320 μL of a 600 mM solution of dienophile **1** or **5** in $CDCl_3$. The samples were then filled up to 600 μL

with $CDCl_3$. The final concentration were catalyst 20 mM and dienophile 0, 5, 10, 20, 40, 80, 160, and 320 mM. The average of the NH signals (**12d**) or the CH_2 signals (**13**) in the proton spectra (7 °C) were applied for the determination of K_a. Calculated shifts were adapted to the experimental values in a nonlinear fitting procedure using K_a as the variable.

Association Studies by ESI-MS. A 1 mM solution of **13** containing 100 equiv of **1** and 100 equiv of **5** was investigated by ESI-MS (injection temperature: 30 °C): *m*/*z* 296.3 (7, $\mathbf{13}^+\cdot\mathbf{5}$), 295.1 (32, $\mathbf{13}^+\cdot\mathbf{5}$), 273.2 (6), 253.2 (10), 241.2 (10), 221.0 (11, $2 \times \mathbf{5} + H^+$), 186.2 (15, $\mathbf{13}^+$), 185.1 (100, $\mathbf{13}^+$). No signal for a complex of **13** and **1** could be observed.

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Supporting Information Available: ^1H NMR data for **2**, **5**, *rac*-**8**, and *rac*-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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