

Size-Selective Catalysis of Ester and Anilide Cleavage by the Dinuclear Barium(II) Complexes of *cis*- and *trans*-Stilbenobis(18-crown-6)

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The basic ethanolysis of esters and anilides endowed with a distal carboxylate anchoring group is catalyzed by the dinuclear Ba(II) complexes of *cis*- and *trans*-stilbenobis(18-crown-6). Comparison with the catalytic efficiency of a mononuclear model catalyst demonstrates that the two metal ions in the dinuclear complexes act synergically. The *cis* form of the catalyst is more efficient than the *trans* form and much more sensitive to the size of the substrate, showing that the concave shape imposed by the *cis* double bond is better suited for catalysis. An experiment in which the less active *trans* form is photoactivated in situ is also reported.

In our previous works we have shown that (i) the basic ethanolysis of esters^{1,2} and amides³ is efficiently catalyzed by alkaline-earth metal ions such as Sr²⁺ and Ba²⁺ and by their complexes with crown ethers and that (ii) the latter complexes can also be used as recognition sites for substrates endowed with a carboxylate anchoring group.⁴ Thus, the dinuclear Ba²⁺ and Sr²⁺ complexes of the ditopic ligand **1** proved to be efficient and selective

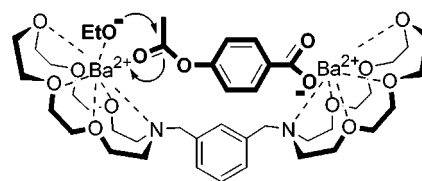
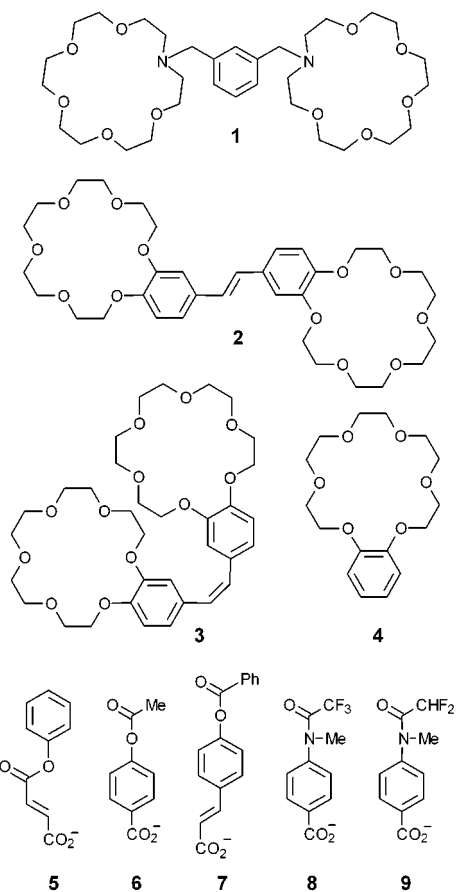


Figure 1. Productive catalyst–substrate complex for the basic ethanolysis of **6**. In the catalyst (**1**·[Ba]₂) one of the metal ions serves as a binding unit for the carboxylate anchoring group and the other binds to ethoxide ion and activates its addition to the ester carbonyl.



catalysts of the basic ethanolysis of esters and amides such as **6** and **8**, which can be anchored to the catalyst through the carboxylate recognition site.^{4,5} From the schematic picture of the productive catalyst–substrate complex shown in Figure 1, it is apparent that a fundamental prerequisite for efficient catalysis is that the target substrate and catalyst must form a well-matched pair in terms of sizes and geometrical features. The couple of structurally simple and easily available bis(crown) stilbene receptors **2** and **3** are here considered as a good testing system for the investigation of size selectivity. The bimetallic complexes of **2** and **3** have virtually identical catalytic and recognition sites⁶ but quite different shapes, as a consequence of the configurational change in the spacer connecting the two crown ether moieties. Although the geometries of both dinuclear catalysts are not rigidly defined, in that they can adjust the mutual arrangement of the recognition and catalytic sites by means of conformational changes of the flexible

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(6) Due to presumably different extents of conjugation of the aryl ether oxygens with the π -system in the two isomers, slightly different interactions of the crown ether moiety with the cation are predictable in the two bimetallic complexes. This effect can nevertheless be reasonably considered unimportant.

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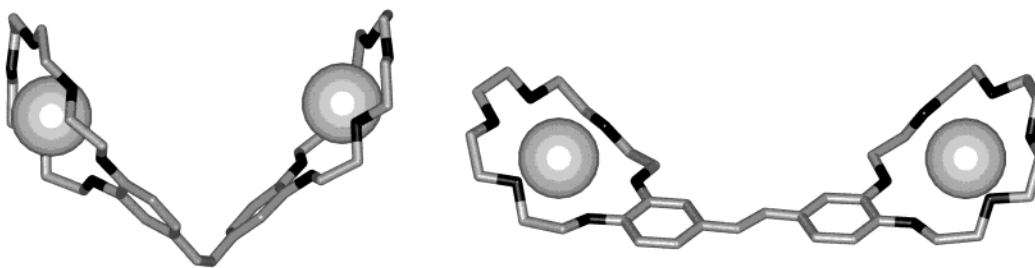


Figure 2. Computer-generated structures of $3 \cdot [Ba]_2$ (left) and $2 \cdot [Ba]_2$ (right).

crown ether moieties and restricted rotations around the essentially single bonds connecting the aromatic rings to the double-bonded carbons, there is no doubt that the bimetallic complex of the cis isomer has a more compact, concave shape, with a narrower gap between the metal centers (Figure 2).

We report here the results of a kinetic investigation of the influence of catalysts $2 \cdot [Ba]_2$ and $3 \cdot [Ba]_2$ in the cleavage of esters **5–7**, in which the distance spanning the carboxylate anchoring group and the reaction site increases in the order $5 < 6 < 7$, and of amides **8** and **9**. The monometallic complex $4 \cdot [Ba]$ has also been investigated as a reference catalyst to probe the synergism of the two metal centers in the bimetallic complexes.

Results and Discussion

Ligand **2** was easily obtained by McMurry reductive coupling of 4'-formylbenzo-18-crown-6.⁷ Photoisomerization of **2** gave the cis isomer **3** in good yield. Complexation and kinetic experiments have been carried out in 85/15 (v/v) EtOH/MeCN at 25 °C. Consistent with the strong complexation ability of benzo-18-crown-6 (**4**) toward Ba^{2+} ion ($K = 10^{5.48} M^{-1}$ in MeOH at 25 °C),⁸ a virtually quantitative formation of the bimetallic complexes $2 \cdot [Ba]_2$ and $3 \cdot [Ba]_2$ has been observed in 85/15 (v/v) EtOH/MeCN. As shown by the spectrophotometric and 1H NMR titration curves of the ditopic receptor **2** (Figure 3), both equilibrium constants for the formation of the 1:1 complex $2 \cdot [Ba]$ and for the conversion of the latter into the bimetallic complex $2 \cdot [Ba]_2$ are too large to measure in this reaction medium. In the case of receptor **3** absorbance variations upon complexation are too small to be useful, but 1H NMR titration definitely shows that formation of the bimetallic Ba^{2+} complex is also in this case virtually quantitative upon addition of 2 mol equiv of $Ba(SCN)_2$ to a 1.00 mM solution of the receptor.

Kinetic data have been obtained in 1.00 mM EtONMe₄ and 0.025 mM substrate solutions, in the absence or presence of additives. The rate data have been summarized in Table 1 for esters **5–7** and in Table 2 for amides **8** and **9**. For experimental convenience in this standard set of reaction conditions the substrate undergoing solvolysis is the less concentrated component of the reaction mixture. Clean first-order kinetics were observed in all cases.

Consistent with previous findings,^{2,3} the presence of Ba^{2+} alone induces significant enhancement of rates of cleavage of both esters and amides. Rate accelerations

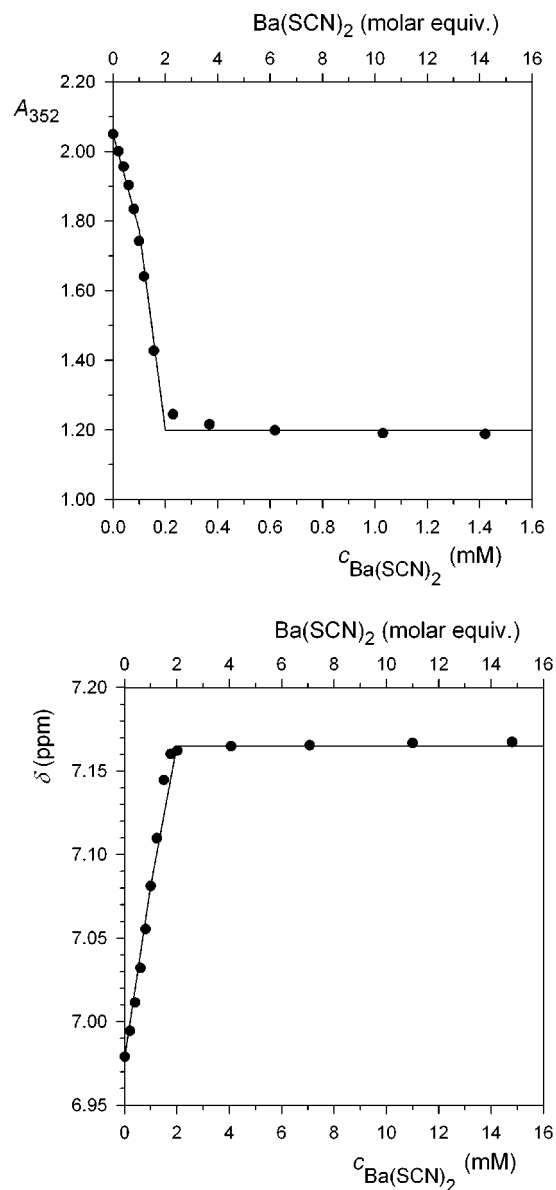


Figure 3. Formation of the bimetallic complex of receptor **2**; (top) spectrophotometric titration of 0.100 mM **2** with $Ba(SCN)_2$ (85/15 EtOH/MeCN (v/v), 25 °C); (bottom) 1H NMR titration of 1.00 mM **2** with $Ba(SCN)_2$ (the chemical shift of the aromatic singlet signal is reported in the ordinate; 85/15 CD_3CD_2OD/CD_3CN (v/v), 25 °C). In both graphs the piecewise lines have been drawn as guidelines connecting the experimental points.

are on the order of 20- to 30-fold (entries 7 and 12 in Table 1; entries 2 and 7 in Table 2), with the exception of ester **5**, whose ethanolysis rate increases by 500-fold (entry 2 in Table 1). The much higher sensitivity of the

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Table 1. Catalysis of the Basic Ethanolysis of Esters 5–7 in 85/15 (v/v) EtOH/CH₃CN at 25 °C^a

entry	ester	additive, mM	k_{obs} (s ⁻¹) ^b	k_{rel}	$k_{\text{ditopic}}/k_{\text{monotopic}}$
1	5		$1.4_6 \times 10^{-4}$	1.0	
2		Ba ²⁺ , 0.20	7.4×10^{-2}	505	
3		4·[Ba], 0.20	3.0×10^{-2}	206	
4	6	2·[Ba] ₂ , 0.10	0.25	1710	8.3
5		3·[Ba] ₂ , 0.10	0.20	1370	6.7
6			8.2×10^{-4}	1.0	
7	7	Ba ²⁺ , 0.20	$2.5_4 \times 10^{-2}$	31	
8		4·[Ba], 0.20	$3.2_6 \times 10^{-2}$	40	
9		2·[Ba] ₂ , 0.10	0.38	460	11.5
10	7	3·[Ba] ₂ , 0.10	3.5	4260	107
11			2.8×10^{-4}	1.0	
12		Ba ²⁺ , 0.20	6.5×10^{-3}	23	
13	7	4·[Ba], 0.20	9.8×10^{-3}	35	
14		2·[Ba] ₂ , 0.10	0.24	860	24.5
15		3·[Ba] ₂ , 0.10	0.69	2450	70.0

^a Experiments carried out on 0.025 mM substrate solutions in the presence of 1.00 mM Me₄NOEt. ^b Error limits on the order of ± 3 –5%.

Table 2. Catalysis of the Basic Ethanolysis of Anilides 8 and 9 in 85/15 (v/v) EtOH/CH₃CN at 25 °C^a

entry	anilide	additive, mM	k_{obs} (s ⁻¹) ^b	k_{rel}	$k_{\text{ditopic}}/k_{\text{monotopic}}$
1	8		4.0×10^{-5}	1.0	
2		Ba ²⁺ , 0.20	7.6×10^{-4}	19	
3		4·[Ba], 0.20	5.6×10^{-4}	14	
4	9	2·[Ba] ₂ , 0.10	2.0×10^{-3}	50	4
5		3·[Ba] ₂ , 0.10	1.3×10^{-2}	335	24
6			3.5×10^{-6}	1.0	
7	9	Ba ²⁺ , 0.20	7.0×10^{-5}	20	
8		4·[Ba], 0.20	5.9×10^{-5}	17	
9		2·[Ba] ₂ , 0.10	1.8×10^{-4}	52	3
10	9	3·[Ba] ₂ , 0.10	9.6×10^{-4}	275	16

^a Experiments carried out on 0.025 mM substrate solutions in the presence of 1.00 mM Me₄NOEt. ^b Error limits on the order of ± 3 –5%.

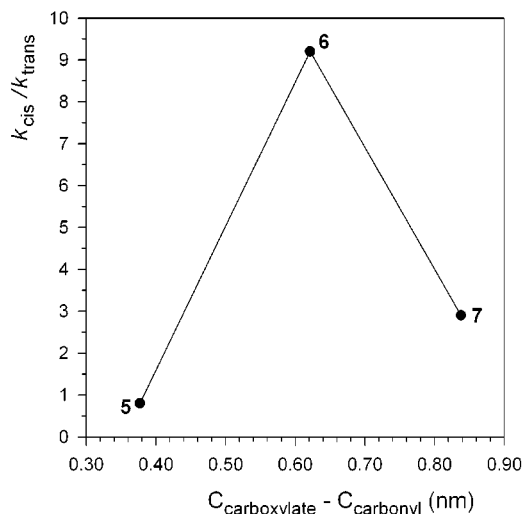
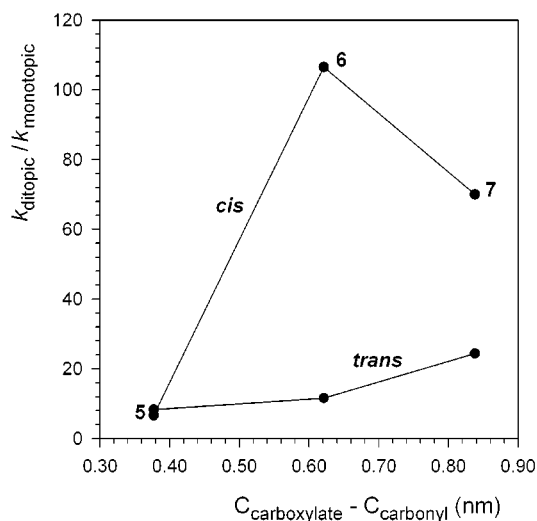
reaction of **5** to the electron-withdrawing influence of the cation-paired carboxylate⁴ is most likely to be ascribed to the fact that its carbonyl group is the closest to carboxylate in the lot of investigated substrates.

Complexation of the metal ion to the monotopic ligand **4** does not produce major changes in the catalytic efficiency (entries 8 and 13 in Table 1; entries 3 and 8 in Table 2). Again the largest influence is seen with substrate **5**, for which there is a significant rate retardation (entry 3 in Table 1) compared to the uncomplexed metal ion.

The bimetallic catalysts are in all cases superior to the metal complex of the monotopic ligand **4**, which emphasizes the importance of synergism of the two metal centers in 2·[Ba]₂ and 3·[Ba]₂, as measured by the $k_{\text{ditopic}}/k_{\text{monotopic}}$ ratios listed in the last column of Tables 1 and 2.

In the ethanolysis of ester **5**, the $k_{\text{ditopic}}/k_{\text{monotopic}}$ ratios are low and very nearly independent of catalyst identity. However, in all the other cases 3·[Ba]₂ is a much more effective catalyst than 2·[Ba]₂, which indicates that the concave shape of the former imposed by the cis double bond is better suited to selective stabilization of the transition state.

A graphical illustration of the requirements of catalysis of ester ethanolysis in terms of substrate size and catalyst shape is given in Figure 4. In the top diagram the $k_{\text{ditopic}}/k_{\text{monotopic}}$ ratios for catalysts 2·[Ba]₂ and 3·[Ba]₂ are plotted versus the carboxylate–carbonyl distance in the ester

**Figure 4.** $k_{\text{ditopic}}/k_{\text{monotopic}}$ ratios (top) and $k_{\text{cis}}/k_{\text{trans}}$ ratios (bottom) as functions of the $C_{\text{carboxylate}}-C_{\text{carbonyl}}$ distance in substrates 5–7.

substrate, taken between the carbon atoms of the two functions. The calculation is straightforward for esters **5** and **6**, while for ester **7** the quoted distance is an average quantity. The quantities k_{cis} and k_{trans} in the bottom diagram are defined as the k_{obs} value measured in the presence of 3·[Ba]₂ and 2·[Ba]₂, respectively. Whereas the catalytic power of the trans form 2·[Ba]₂ is relatively low and increases monotonically on increasing the size of the substrate, the cis form 3·[Ba]₂ exhibits a structured profile, with a pronounced maximum at substrate **6**. A corresponding maximum is seen in the $k_{\text{cis}}/k_{\text{trans}}$ profile (bottom plot of Figure 4).

It is apparent that the cis form 3·[Ba]₂ is much more sensitive to the size of substrate than the trans form 2·[Ba]₂ and that the best substrate–catalyst combination is that between ester **6** and 3·[Ba]₂, in both synergism between the metal centers and cis/trans selectivity.

Both dinuclear complexes 2·[Ba]₂ and 3·[Ba]₂ are much poorer catalysts for anilides than for esters. This is presumably related to the more strict geometrical requirements of amide ethanolysis, in which a metal-coordinated solvent molecule acts as a general acid catalyst for expulsion of the aniline leaving group in the rate-determining step.³ As already observed in the cleavage of the corresponding ester substrate **6** and in the

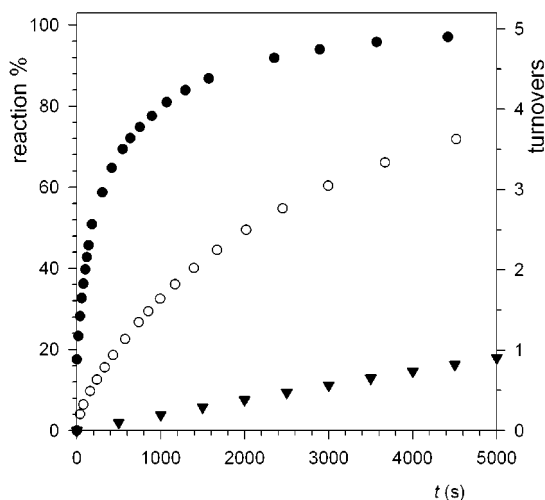


Figure 5. Turnover catalysis of ethanolsis of 0.50 mM anilide **8** by $3\cdot[Ba]_2$ in the presence of 1.00 mM EtONMe₄: (▼) ethoxide alone; (○) ethoxide plus 0.20 mM Ba²⁺; (●) ethoxide plus 0.10 mM $3\cdot[Ba]_2$.

cleavage of amide **8** and of the less activated amide **9**, the best geometrical match has been found with the *cis* bimetallic catalyst $3\cdot[Ba]_2$. The latter is indeed ca. 6 times more efficient than the *trans* isomer with both amides, an effect comparable to the 9.3-fold rate enhancement observed in the cleavage of ester **6**.

Complexes $2\cdot[Ba]_2$ and $3\cdot[Ba]_2$ are genuine turnover catalysts, as shown by the typical set of experiments plotted in Figure 5. A 5-fold molar excess of anilide **8** is completely ethanolyzed in the presence of $3\cdot[Ba]_2$ at a rate that is much higher than those measured in blank experiments. The catalyst $3\cdot[Ba]_2$ brings about at least five turnovers, but its efficiency is limited by product inhibition, as anticipated on the basis of previous studies⁴ and confirmed by the shape of the reaction profile.

The superior catalytic power of $3\cdot[Ba]_2$ compared to that of $2\cdot[Ba]_2$ suggested an experiment in which the less active $2\cdot[Ba]_2$ is activated *in situ* by photoisomerization into the more active $3\cdot[Ba]_2$ in the time course of the reaction. The experiment reported in Figure 6 was started in the spectrophotometric cell compartment and the reaction progress monitored in the early stages. After 40 s the cuvette was removed from the spectrophotometer and rapidly introduced into a photoreactor, where it was irradiated for 30 s.⁹ The cuvette was then rapidly reintroduced into the spectrophotometer and the reaction progress monitored until reaction completion. Figure 6 clearly shows that the catalytic efficiency significantly increases upon irradiation and that the reaction profile is close to the calculated one for the photostationary state of the reaction mixture. Although there is no way to revert either thermally or photochemically to the original, less active state,¹⁰ this experiment strongly suggests that realization of a photoswitchable supramolecular catalyst is a practical proposition.

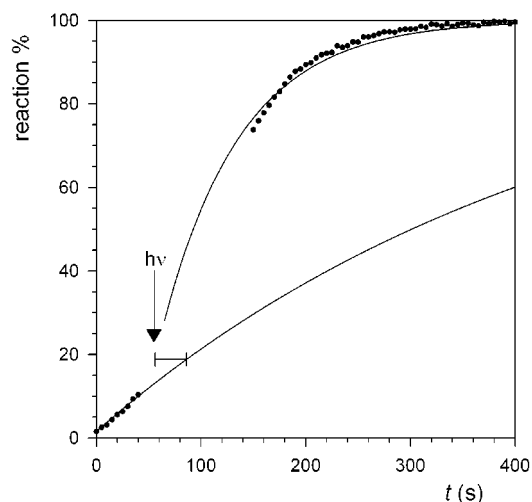


Figure 6. *In situ* photoactivation of the catalyst $2\cdot[Ba]_2$ in the time course of the basic ethanolsis of anilide **8**. Reaction conditions: 1.00 mM EtONMe₄, 0.10 mM $2\cdot[Ba]_2$, 0.025 mM **8**, 85/15 (v/v) EtOH/CH₃CN, 25 °C. The arrow indicates the start of the irradiation, whose duration is given by the horizontal bar. The time–concentration profiles are calculated with the pertinent k_{obs} values given in Table 2.

Experimental Section

Instruments and Materials. ¹H and ¹³C NMR spectra were recorded at 300 and at 75 MHz, respectively. Chemical shifts are reported in ppm from tetramethylsilane, added as internal standard. The reactor used for the photoisomerization of receptor **2** into receptor **3** was equipped with 16 25 W lamps, for a total of 400 W, with an emission maximum at 300 nm. Acetonitrile (HPLC Plus grade) was used in the preparation of the reaction medium. A commercial sample of 18-crown-6 (**4**) was used as such. *trans*-Stilbenobis(18-crown-6) (**2**) was prepared by reductive coupling of 4'-formylbenzo-18-crown-6⁷ with TiCl₄/Zn in THF according to a literature procedure.⁷ *cis*-Stilbenobis(18-crown-6) (**3**) was obtained by photoinduced isomerization of **2** in 85/15 EtOH/CH₃CN.⁷ Compounds **5**·H⁺,¹¹ **6**·H⁺,¹² **7**·H⁺,¹³ and **8**·H⁺¹⁴ were prepared as reported in the literature.

4-[Methyl(difluoroacetyl)amino]benzoic Acid (9·H⁺). Difluoroacetic anhydride¹⁵ (1.65 g, 9.48 mmol) was added dropwise under an argon atmosphere to a rapidly stirred suspension of 4-(methylamino)benzoic acid (0.650 g, 4.3 mmol) in chloroform (9 mL) at room temperature. Stirring was prolonged for an additional 45 min, and then water (4.30 mL) was added to destroy excess anhydride. The two phases were separated, and the organic layer was washed with water. Chloroform was evaporated, and to eliminate water the solid residue was repeatedly treated with benzene and evaporated to dryness. The crude product (0.56 g) was recrystallized from benzene (20 mL) to obtain **9**·H⁺ (0.50 g, 2.44 mmol, 57% yield) as a white solid (mp 145–147 °C).

¹H NMR (CD₃COCD₃): 8.15 (2H, d, *J* = 8.6 Hz), 7.58 (2H, d, *J* = 8.6 Hz), 6.12 (1H, t, 53.5 Hz H–F spin coupling), 3.36 (3H, s). ¹³C NMR (CD₃COCD₃): 166.75, 161.87, 146.90, 131.97, 129.07, 128.48, 107.25, 37.77. Anal. Calcd for C₁₀H₉F₂NO₃: C, 52.41; H, 3.96; N, 6.11. Found: C, 52.81; H, 4.15; N, 5.91.

Substrates **5**–**9** were generated *in situ* by neutralization of the parent acids with Me₄NOEt.

Other materials, apparatuses, and techniques were as reported previously.⁴

(9) The irradiation time was optimized in order to reach the photostationary state containing 90% of the *cis* form of the catalyst while minimizing the decomposition of the receptor into phenanthrene derivatives (see: Leigh, W. J.; Lewis, T. J.; Lin, V.; Postigo, J. A. *Can. J. Chem.* **1996**, *74*, 263).

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Equilibrium and Rate Measurements. UV titrations of **2** and **3** with $\text{Ba}(\text{SCN})_2$ were carried out on a double-beam spectrophotometer. Kinetic measurements were carried out in the thermostated cell compartment of a diode array spectrophotometer or in a stopped-flow system in the case of the basic ethanolysis of substrate **6** when carried out in the presence of the catalyst $\mathbf{3} \cdot [\text{Ba}]_2$. All rate constant values reported in Tables

1 and 2 have been obtained from full time courses fitted to a first-order rate equation.

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