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Chiral *N*-Alkyl-2,4,6-triphenylpyridiniums as Enantioselective Triplet Photosensitizers. Laser Flash Photolysis and Preparative Studies[†]

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Three *N*-alkylpyridinium photosensitizers having chiral alkyl groups have been prepared by reacting 2,4,6-triphenylpyrylium tetrafluoroborate ion with (1*R*,2*S*)-(−)-norephedrine, (*S*)-(+)-2-(aminomethyl)pyrrolidine, and (*R*)-(−)-1-cyclohexylethylamine. Laser flash photolysis allows detection of the corresponding triplet excited states that are quenched by hydrogen atom donors and electron donors. Asymmetric quenching of the chiral triplet excited state was observed using enantiomerically pure 1,2-diamino cyclohexane as quencher. Low enantiomeric excess values (up to 7%) were measured for the photochemical cyclization of 5-methyl-4-hexenoic acid to its corresponding γ-lactone using these chiral *N*-alkylpyridinium as photosensitizers.

Introduction

Asymmetric induction in photochemical reactions is a topic of much current interest.[1,2] In comparison with enantioselective catalytic reactions, photochemical reactions have in principle the advantages that they can be performed at low temperatures and do not require the use of an elaborate chiral catalyst that very frequently needs dedicated synthesis to be prepared. The most general methodology to induce enantioselectivity in photochemical reactions consists of the solid-state irradiation of crystals containing a chiral quaternary ammonium cation as ionic auxiliary and a photolabile aromatic carboxylate.[3−9] Although the enantiomeric excesses (ee) reported using the chiral ammonium auxiliary approach in the solid state are in many cases impressive, this strategy suffers from the limitation that co-crystallization of the chiral auxiliary and the photoreactive substrate is a prerequisite. It would be experimentally much simpler if the concept of ionic auxiliary could be effected in solution rather than for single crystals. Among the different approaches to effect enantioselective photochemical reactions in solution, those using a chiral photosensitizer have given the best results. Most of the work published on this topic has used energy transfer photosensitizers derived from polyalkyl benzenepolycarboxylates, wherein the chirality resides in the alkyl groups.[10−13] Besides energy transfer, photoinduced electron transfer is another general type of sensitized photochemical reactions. However, in contrast to energy transfer, the use of a chiral photosensitizer for asymmetric photoinduced electron transfer has been comparatively much less studied, with the use of 2,2′-dicyano-1,1′-binaphthyl as the most relevant example.[14] In view of these precedents, it would be of much interest to explore the efficiency of other chiral electron-transfer photosensitizers to perform asymmetric photochemical reactions. In the present work, we report a simple and general synthetic route to obtain chiral *N*-alkyl-substituted 2,4,6-triphenylpyridiniums. The photochemical properties of these dyes as photosensitizers have been studied by means of laser flash photolysis, and a preliminary study on the performance of these pyridinium ions to induce chirality in photochemical reactions has been carried out.

Results and Discussion

Chiral *N*-alkyl-2,4,6-triphenylpyridiniums (**1**−**3**) where the alkyl chain has an asymmetric carbon can be easily prepared by stirring at moderate temperature a solution

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[†] Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday.

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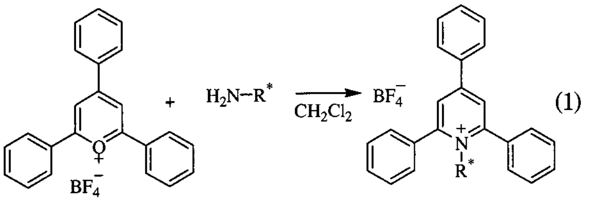
of commercially available 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) in CH_2Cl_2 in the presence of equimolar amounts of a primary amine (eq 1).



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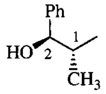
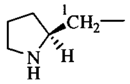
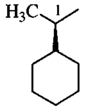
1	
2	
3	

Given the large number of primary amines in the chiral pool, the reaction depicted in eq 1 is very general and can be applied for the preparation a large number of chiral pyridiniums. Therein, we have prepared three representative examples in which the *N*-alkyl chain contains a hydroxy group (**1**), an amine group (**2**), or exclusively a hydrocarbon (**3**).

On the other hand, the presence of phenyl substituents on the pyridinium ring should shift the λ_{max} of the parent pyridinium absorption to longer wavelengths while increasing the molar absorptivity of the photosensitizer. The λ_{max} of a photosensitizer is a key parameter since it has to make possible the selective excitation of the photosensitizer in the presence of a wide range of substrates.

The course of the transformation of TPT into the corresponding *N*-alkylpyridinium could be conveniently followed by recording the transmission UV–vis spectra of the reaction mixture at different reaction times. In these spectra, a gradual decrease of the intensity of the characteristic TPT bands at 370 and 420 nm is observed. This disappearance is concomitant with the growth of a band at 325 nm common for the three *N*-alkylpyridinums (**1**–**3**). As the reaction of TPT to pyridiniums progresses, there is within the experimental error an isosbestic point in the UV–vis spectra at 350 nm (Figure 1). Noteworthy is the fact that the λ_{max} of the *N*-alkylpyridinium is longer than 300 nm, which allows the use of Pyrex glassware that can be used as a cutoff filter, making simple the experimental set up for the photosensitizing reactions using *N*-alkylpyridiniums. For *N*-alkylpyridiniums λ_{max} is around 280 nm.[15]

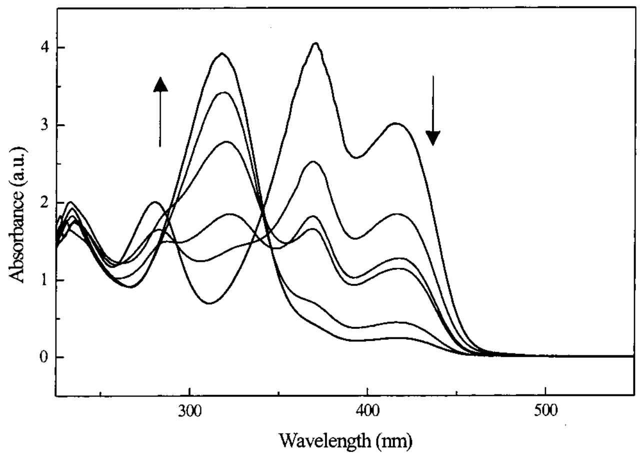


FIGURE 1. UV–vis spectra of an equimolar mixture of TPT (0.02 M) and (1*R*,2*S*)-(−)-norephedrine in CH_2Cl_2 recorded at increasing reaction times. The decrease of the bands at 370 and 420 nm correspond to the disappearance of TPT and the band at 325 nm to the formation of 2,4,6-triphenylpyridinium **1**.

When the characteristic TPT bands have a negligible intensity in the UV, the reaction was stopped and the solvent removed under reduced pressure. After removal of the solvent, the resulting *N*-alkylpyridiniums were recrystallized in ethanol and characterized analytical and spectroscopically before studying their photochemistry and the degree of enantioselective quenching with (1*R*,2*R*) and (1*S*,2*S*)-1,2-diaminocyclohexane.

The most characteristic common feature of the three chiral pyridiniums (**1**–**3**) in the ^1H NMR spectra was a singlet at 7.6 ppm corresponding to the two protons at the 3 and 5 positions of the pyridinium ring. The signals corresponding to the three phenyl rings also appeared between 7.6 and 7 ppm. In IR spectroscopy, the bands due to the stretching vibration of the aromatic rings were observed, with the peak at 1489 cm^{-1} being ascribed as specific for *N*-alkylpyridiniums.[16] The mass of the pyridinium cation was acertained by FAB-MS, where the BF_4^- counteranion did not appear. A definite confirmation of the structure of pyridinium **1** was obtained by single-crystal X-ray diffraction (see Figure S1 in the Supporting Information).

The chiral *N*-alkylpyridinium salts were submitted to laser flash photolysis at 266 nm in acetonitrile solution (10^{-4} M) under dynamic flow. Dynamic flow ensures the exposure of fresh sample to each laser shot, thus avoiding the interference of any photolysis product (i.e., compound **1**, in which a 15% of photodegradation after 4 h, with formation of benzaldehyde, was observed). Representative transient spectra recorded 1.5 μs after the laser flash are presented in Figure 2. Spectra have in common two absorption bands around 370 and 450 nm. In the photolysis of **1**, bleaching of the pyridinium ground state (negative signal around 320 nm) was also observed. This bleaching is not apparent in the cases of **2** and **3**, for which disappearance of the ground state should also occur. The failure to observe bleaching is due probably

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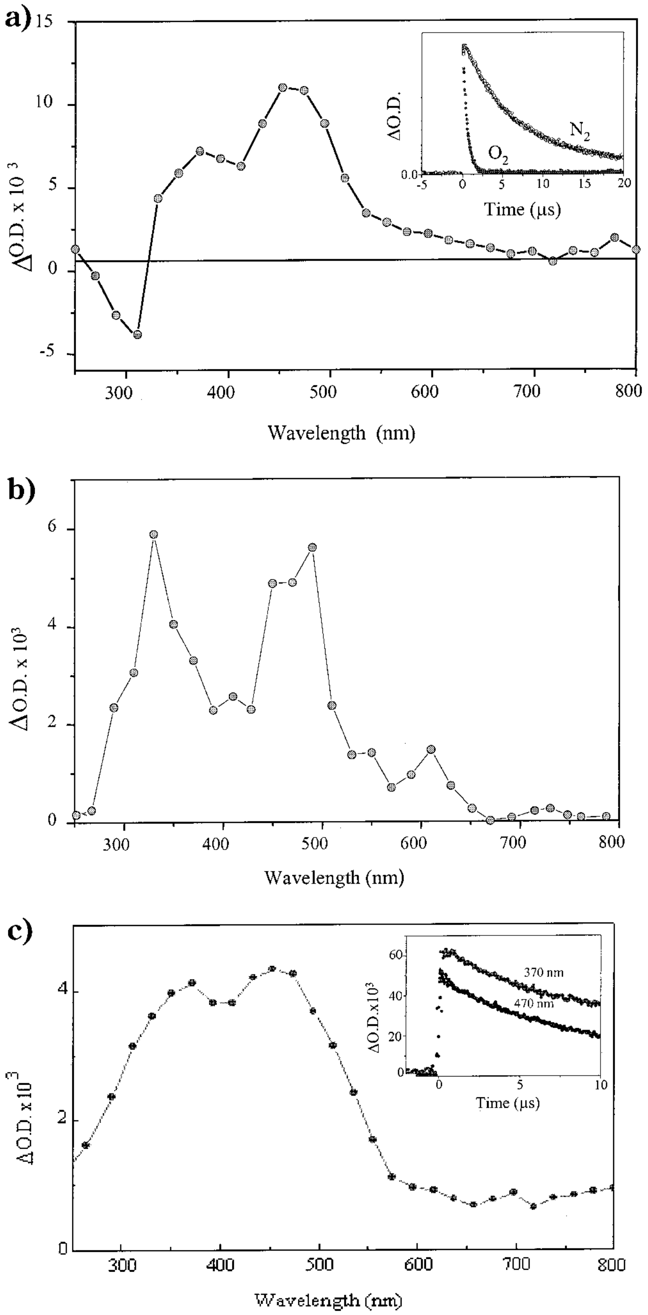


FIGURE 2. (a) Transient spectrum 1.5 μs after 266 nm excitation of a solution of **1** (10^{-4} M) in acetonitrile after N_2 purging. The spectrum has been recorded under dynamic flow. The insert shows the temporal signal profile recorded at 450 nm for pyridinium **1** upon 266 nm laser excitation after N_2 or O_2 purging. (b) Transient spectrum 1.5 μs after 266 nm excitation of a solution of **2** (10^{-4} M) in acetonitrile after N_2 purging. (c) Transient spectrum 1.5 μs after 266 nm excitacion of a solution of **3** (10^{-4} M) in acetonitrile after N_2 purging. The insert shows the temporal signal profiles monitored at 370 and 470 nm for a N_2-purged pyridinium **3** (10^{-4} M) in acetonitrile after 266 nm laser excitation.

to the fact that the transient absorptions are somewhat shifted to shorter wavelengths and overlap with the ground-state absorption. This overlapping masks the observation of bleaching (negative absorption) for compounds **2** and **3**.

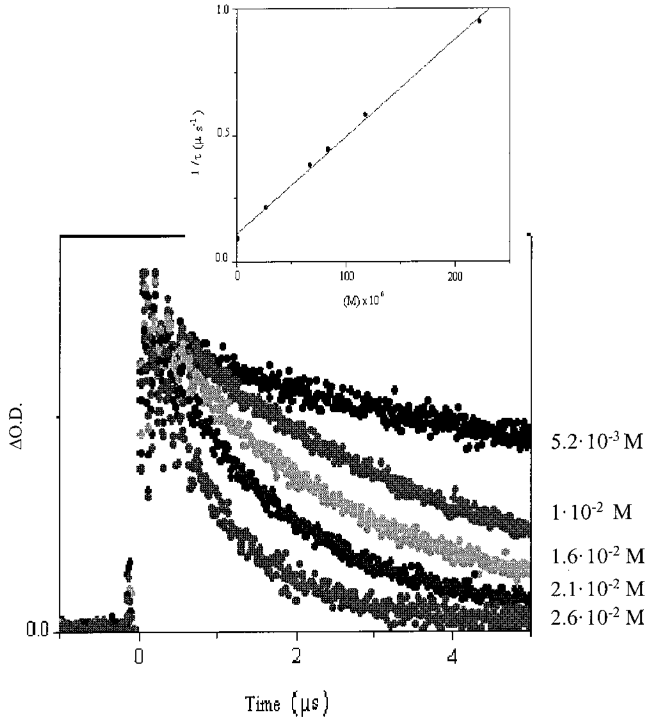
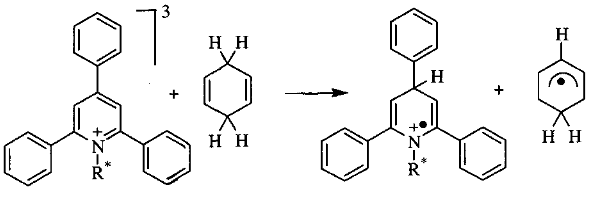


FIGURE 3. Signal decay monitored at 450 nm of a N_2-purged sample of pyridinium **1** upon 266 nm laser excitation in the presence of increasing amounts of 1,4.cyclohexadiene (for concentrations see the figure). The inset shows the Stern–Volmer plot of the rate constant vs the quencher concentration.

The two absorption bands observed in Figure 2 correspond to the same transient as evidenced by the same temporal profile of the signal (Figure 2c) and their response against quenchers. This transient can be attributed to the *N*-alkylpyridinium triplet excited state based on the influence of oxygen (Figure 2a) in agreement with previous reports on the laser flash photolysis of structurally related pyridiniums.[17]

The *N*-alkylpyridinium triplet excited state is also quenched by hydrogen atom donors such as 1,4-cyclohexadiene (Figure 3) with quenching rate constants (k_q) ranging from 3.3×10^8 to 1×10^{10} M^{-1} s^{-1} depending on the alkyl group attached to the aromatic N atom. This quenching most probably follows eq 2.



(2)

According to this equation, a radical cation should be formed. In fact, a close inspection of the signal at 450 nm corresponding to the triplet and at 350 nm shows a decay and a growth, respectively, occurring at the same kinetics (Figure 4). These signals can be interpreted as the disappearance of the triplet and the formation of the aminyl radical cation as indicated by eq 2. However, the

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[17] Marciniak, B.; Hug, G. L.; Rozwadowski, J.; Bobrowski, K. *J. Am. Chem. Soc.* **1995**, *117*, 127–34.

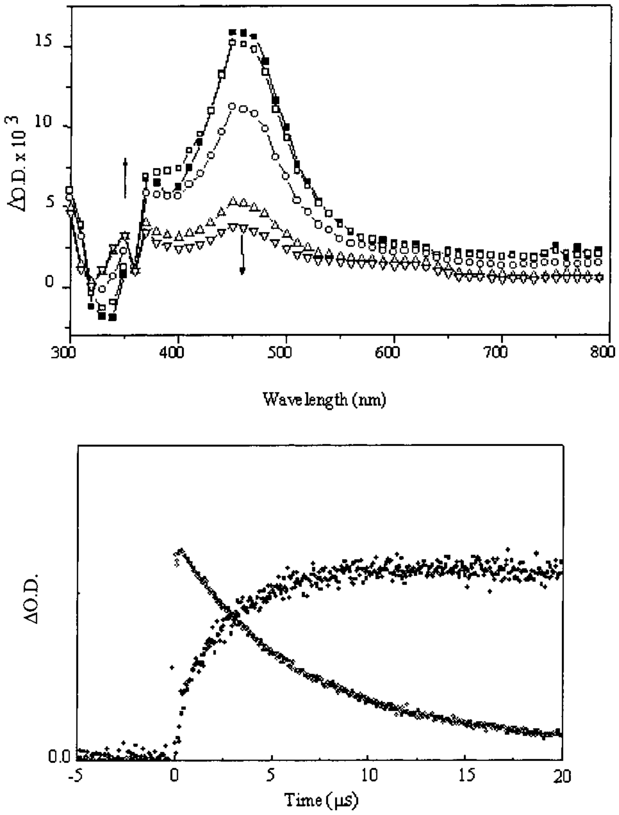
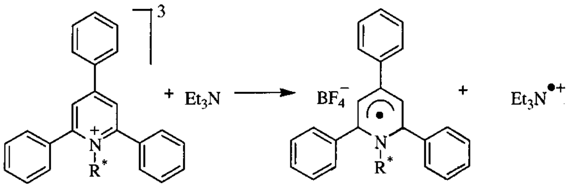


FIGURE 4. (Top) Transient spectra recorded at 0.25, 0.5, 2.5, 6, and 25 μs after 266 nm excitation of a N_2-purged sample of pyridinium **1** in the presence of 1,4-cyclohexadiene (5.2×10^{-3} M). (Bottom) Temporal signal profiles monitored at 350 and 475 nm of the same sample and conditions as above.

low intensity of the signal and the fact that 350 nm is a wavelength close to the ground-state absorption and to one of the triple absorption bands complicates considerably recording the authentic spectrum of these radical cations. Nevertheless, what is clear from Figure 4 is that one transient grows at the expense of the decay of other transient. Obviously, the secondary transient assigned to the aminyl radical cation is much longer lived than the primary triplet from which it derives.

The triplet excited state of pyridiniums **1**−**3** is also quenched by amines most probably through an electron-transfer mechanism recording to eq 3. The resulting radical has a transient spectrum (Figure 5) that is different from that of the precursor triplet excited state.



(3)

As indicated in the Introduction, our goal was to develop a series of chiral electron-transfer photosensitizers that could be obtained from readily available starting materials through a very simple synthetic procedure. Thus, the degree of chiral discrimination exhibited by the chiral triplet excited state of the *N*-alkylpyridinium remains to be seen. This was tested by adding (1*R*,2*R*) and (1*S*,2*S*) enantiomers of the 1,2-diaminocyclohexane. As anticipated in view of the quenching by triethylamine and the electron-acceptor ability exhibited by pyridiniums, the two enantiomers of the 1,2-diaminocyclohexane were able to quench the pyridinium excited state with quenching rate constants that were different for each 1,2-diaminocyclohexane enantiomer. Figure 6 shows the actual Stern−Volmer plots for each pyridinium, and the data are collected in Table 1. The most salient feature is that the chiral discrimination expressed as the relative difference between the quenching rate constant for each enantiomer of 1,2-diaminecyclohexane depends on the alkyl chain attached to the aromatic nitrogen. The pyridinium derived from (1*R*,2*S*)-(−)-norephedrine is the one exhibiting a more enantioselective quenching, remarkably higher than that of the pyridium derived from (1*R*)-(−)-1-cyclohexylethylamine (62.3, 21.6, 22.0% for **1**, **2**, or **3**, respectively). The better chiral recognition of **1** and 1,2-diaminocyclohexane can be due to the presence of two chiral groups on the *N*-alkyl chain of **1** or to the relative bulkiness of the group derived from norephedrine. These results open the possibility that other related chiral pyridiniums exhibit a higher enantioselective discrimination following the methodology developed here. In principle, the key and lock fit between the chiral quencher and the photosensitizer seems the most important factor influencing the quenching rate constants.

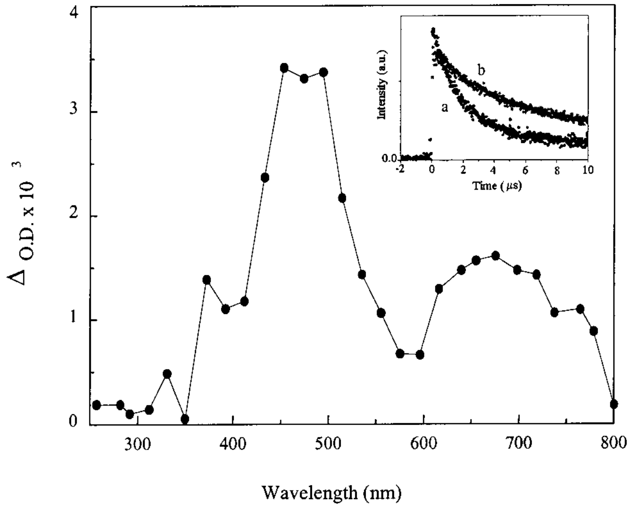


FIGURE 5. Transient spectrum after N_2 purging and 266 nm excitation of a 10^{-4} M acetonitrile solution of pyridinium **1** in the presence of 0.8×10^{-3} M of triethylamine. The spectrum has been recorded at 1.5 μs. The inset shows the signal decays monitored at 450 nm in the absence (a) and presence (b) of triethylamine.

To determine to what extent the enantioselective electron-transfer quenching of chiral *N*-alkylpyridiniums can be used to induce asymmetry photochemically, the photosensitized lactone formation of the 5-methyl-4-hexenoic acid (**4**) (eq 4) was carried out in the presence of pyridinium **1**−**3**. This photochemical cyclization has been reported to use cyanoaromatics as photosensitizer,[18]

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[18] Gassman, P. G.; Boltorff, K. J. *J. Am. Chem. Soc.* **1987**, *109*, 7547−7548. Gassman, P. G.; De Silva, S. A. *J. Am. Chem. Soc.* **1991**, *113*, 9870−9872.

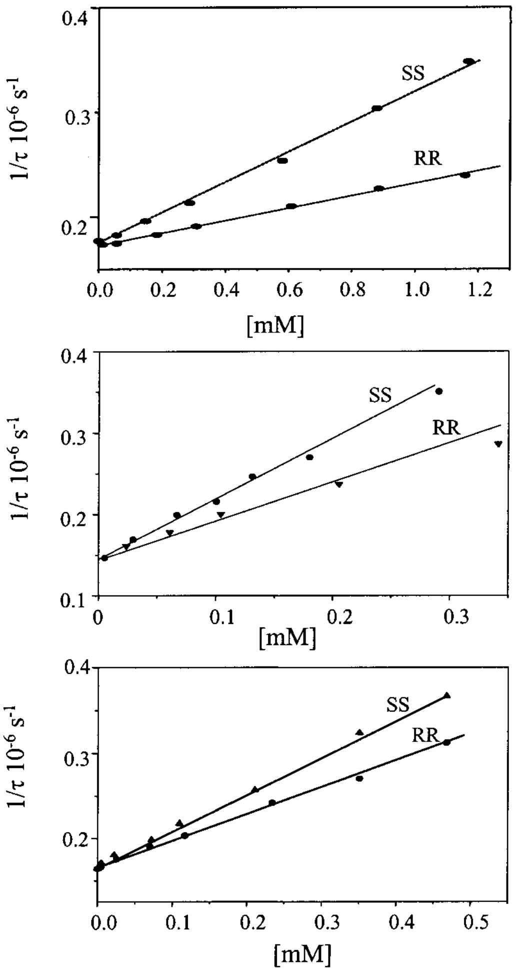
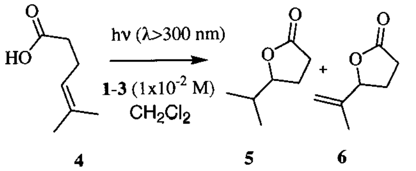


FIGURE 6. Stern–Volmer plots of the quenching rate constants versus the quencher concentration for pyridiniums **1** (top), **2** (middle), and **3** (bottom) using (1*R*,2*R*) and (1*S*,2*S*)-1,2-diaminocyclohexane as quenchers.

and it was demonstrated that this process occurs through an electron-transfer mechanism. Given the structural similarity of TP^+ with our pyridinium photosensitizers and the fact that the reaction can be carried out using Pyrex as filter due to the low absorbance of the β,γ-unsaturated acid, we anticipated that the same cyclization would be promoted by pyridiniums **1**–**3**.



(4)

As expected, photosensitized irradiation of 5-methyl-4-hexenoic acid (0.01 M) in CH_2Cl_2 using pyridiniums **1**–**3** (0.01 M) under N_2 through Pyrex gives predominantly the saturated lactone (**5**) accompanied by lesser amounts of the unsaturated derivative (**6**). A blank control shows that no thermal or photochemical cyclization of **4** occurs in the absence of photosensitizer under the experimental conditions. This clearly demonstrates that the process studied is a photosensitized reaction ruling out direct photolysis of **4**. However, although the enantiomeric excess (ee) values measured by a GC chiral column are sometimes higher than the experimental error, they were below 10%. Table 1 collects the actual ee values measured for this photosensitized process. Again, pyridinium **3** gave the lowest ee value.

In summary, although it is obvious that the results presented are yet far from any practical use and much improvement is still needed, we have demonstrated that a general procedure based on a very simple reaction carried out at moderate temperatures can be use to prepare a wide range of chiral photosensitizers capable to promote photoinduced electron-transfer reactions. Chiral discrimination is clearly observed by photophysical techniques, and the degree of asymmetric recognition clearly depends on the alkyl chain. However, from a preparative point of view, this asymmetric induction is still inefficient and further improvement is required.

Experimental Section

FT-IR spectra were recorded in KBr disks at room temperature. ^1H NMR spectra were recorded in $CDCl_3$ as a solvent and TMS as a internal standard. FAB-MS spectra were performed in nitrobenzyl alcohol matrix. The elemental C, H, N was obtained by combustion chemical analysis. $[\alpha]^{26}_D$ were measured on CH_2Cl_2 solutions (10^{-2} M).

Synthesis of *N*-Alkyl-2,4,6-pyridiniums. Compounds **1**–**3** were prepared by stirring magnetically a solution of the tetrafluoroborate salt of TP^+ (Aldrich) (250 mg) in CH_2Cl_2 (20 mL) to which 1 equiv of the corresponding primary amine (95.2 mg for (1*R*,2*R*)-(−)-norephedrine, 63.0 mg for (*S*)-(+)-2-(aminomethyl)pyrrolidine, and 80.0 mg for (*R*)-(−)-1-cyclohexylethylamine was added. The solution was maintained at room temperature (for **1** and **2**) or at 65 °C (for **3**) for 8 h. The course of the reaction was followed by UV–vis spectroscopy. When the reaction was complete, the solvent was removed under reduced pressure and the solids were recrystallized from ethanol.

Spectroscopic Data for Compounds 1–3. Compound 1. IR (KBr, cm^{-1}): 3052, 1615, 1584, 1563, 1489, 1450, 1063, 768, 694, 526. ^1H NMR (δ, $CDCl_3$): 1.18 (d, 3H, $J = 6.9$ Hz), 4.95 (d, 1H, $J = 6.3$ Hz), 5.28 (m, 1H), 7.05–7.20 (m, 5H), 7.40–7.64 (m, 17H). FAB-MS (*m*/*z*): 442 ($M^{\bullet+}$), 308 (M − 134). Anal. Calcd for $C_{32}H_{28}NOBF_4{\cdot}H_2O$ (528.81): C, 70.22; H, 5.50; N, 2.56. Found: C, 69.53; H, 5.74; N, 2.41. $[\alpha]^{26}_D = +82.5$.

Compound 2. IR (KBr, cm^{-1}): 3052, 2947, 2857, 1615, 1552, 1489, 1450, 1089, 1063, 768, 694, 521. ^1H NMR (δ, $CDCl_3$): 1.01 (m, 2H), 1.38 (m, 2H), 2.15 (m, 1H) 2.62 (m, 1H), 3.15 (m, 1H), 4.40 (t, $J = 15$ Hz, 1H), 4.72 (t, $J = 14.9$ Hz, 1H) 7.60–8.36 (m, 17H). FAB-MS (*m*/*z*): 391 ($M^{\bullet+}$), 308 (M − 83). Anal. Calcd for $C_{28}H_{27}N_2BF_4{\cdot}H_2O$ (495.81): C, 67.76; H, 5.84; N, 5.64. Found: C, 67.80; H, 6.08; N, 6.09. $[\alpha]_D^{26} = +71.3$.

Compound 3. IR (KBr, cm^{-1}): 2950, 2860, 1615, 1553, 1489, 1450, 1063, 768, 694. ^1H NMR (δ, $CDCl_3$): 1.68 (d, 3H, $J = 7.08$ Hz), 0.85–1.86 (m, 11H), 4.75 (m, 1H), 8.69–7.62 (m, 17H). FAB-MS: 418 ($M^{\bullet+}$), 308 (M − 110). Anal. Calcd for $C_{31}H_{32}NBF_4{\cdot}2H_2O$ (540.81): C, 68.78; H, 6.65; N, 2.59. Found: C, 67.94; H, 6.31; N, 2.52. $[\alpha]_D^{26} = -45.3$.

Laser Flash Photolysis. The fourth harmonic of a Nd:YAG laser (266 nm/>10 mJ/pulse, 7 ns/pulse) was used. The transient spectra were obtained by charging a reservoir (250 mL) with an acetonitrile solution of the pyridinium (0.2 o.d. at 266 nm) and flushing the solution through a quartz cell. The solutions were purged with N_2 or O_2 at least 15 min before the laser experiments. The system used a 75 W Hg-doped xenon lamp as monitoring light and 9 dynode electromultipler as detector coupled with a dichronic monochromator. The available wavelength range is from 250 nm to 800 nm. The data were digitized using at Tektronix TDS640A oscilloscope and transferred to a PC that controls the experiment.

TABLE 1. Photophysical Kinetic Data and Enantioselective Recognition Data for Pyridiniums 1−3

	triplet excited state		quenching rate constant (k_q) (M^{-1} s^{-1}) quencher			
photosensitizer	λ_{max} (nm)	lifetime (μs)	1,4-cyclohexadiene	(S,S)-amine	(R,R)-amine	lactone ee[a] (%)
1	370, 450	6.3	3.5×10^9	1.78×10^8	6.7×10^7	5
2	340, 470	10	1×10^{10}	8.3×10^8	6.5×10^8	7
3	370, 450	7.3	3.3×10^8	4.5×10^8	3.4×10^8	3

[a] Irradiation of 5-methyl-4-hexenoic acid (0.01 M) in CH_2Cl_2 in the presence of photosensitizers **1**−**3** at room temperature under N_2. Estimated error ±3.

Steady-State Irradiation. 5-Methyl-4-hexencarboxylic acid (0.1 mmol) was irradiated in a CH_2Cl_2 solution (10 mL) in the presence of chiral *N*-alkylpyridiniums (**1**−**3**) (0.1 mmol). The solutions were purged with N_2 15 min before irradiation. The photolysis was performed at room temperature using Pyrex filtered light ($\lambda \geq 300$ nm) from a medium-pressure 125 W mercury lamp equipped with an outer jacket refrigerating system. At the end of the reaction, the reaction products were analyzed by GC (HP, 5% phenylmethyl silicone, 30 m), GC−MS, and ^{1}H NMR spectroscopy. The identify of the product was confirmed by comparison with an authentic sample prepared by reaction of isobutyraldehyde and ethyl acrylate in the presece of SmI_2 as indicated in ref 19. The ee values were determinated by capillary column G-PN (Chiraldex, γ-cyclodextrin, propionyl) with FID as detector.

Acknowledgment. Financial support by Spanish DGES (Grant No. MAT 00-1768-CO2-01) is gratefully acknowledged. We thank Mrs. B. Ferrer for single-crystal X-ray diffraction.

Supporting Information Available: An ORTEP model of pyridinium **1** obtained from the single-crystal X-ray diffraction (Figure S1). This material is available free of charge via the Internet at http://pubs.acs.org.

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