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Studies on the Enantioselective Catalysis of Photochemically Promoted Transformations: "Sensitizing Receptors" as Chiral Catalysts

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Received October 1, 2002

A strategy for the enantioselective catalysis of photomediated reactions in solution is described, involving the use of chiral molecular receptors possessing appendant triplet-sensitizing moieties. Energy transfer is selectively directed to bound substrate as a consequence of the distance dependence of triplet−triplet energy transfer. This effect, which is equivalent to a binding-induced rate enhancement, enables substoichiometric chirality transfer from the receptor template to the substrate, as observed in the intramolecular enone-olefin photo[2 + 2]cycloaddition of a quinolone substrate.

Introduction

Many important classes of chemical transformations exist for which catalytic enantioselective variants do not exist or have not been optimally developed. Photocycloadditions represent a powerful means of stereogenic C−C and C−O bond formation that have found extensive use in synthesis,[1] yet generally effective strategies for catalytic asymmetric induction in photochemically mediated transformations are largely undeveloped.[2] Thus far, methods affording useful enantiomeric excess have been restricted to *stoichiometric* chirality transfer from preexisting stereocenters in the substrate[3] and the use of chiral auxiliaries[4] (i.e., diastereoselection), solid-state photochemical transformations[5] including clathrates,[6] and unimolecular photochemical reactions in chirally modified zeolites.[7] Most recently, chiral molecular receptors have been shown to serve as highly effective "noncovalent chiral auxiliaries" for enantioselective photo[2 + 2]cycloadditions.[8]

The use of asymmetric media (e.g., chiral solvents,[9] chiral liquid crystalline phases,[10] and chiral polymer matrixes[11]) embodies another approach to stoichiometric chirality transfer in photomediated transformations.[12] However, in contrast to photochemical reactions that take place in the well-defined chiral microenvironment of noncentrosymmetric crystal lattices[13] and synthetic host−

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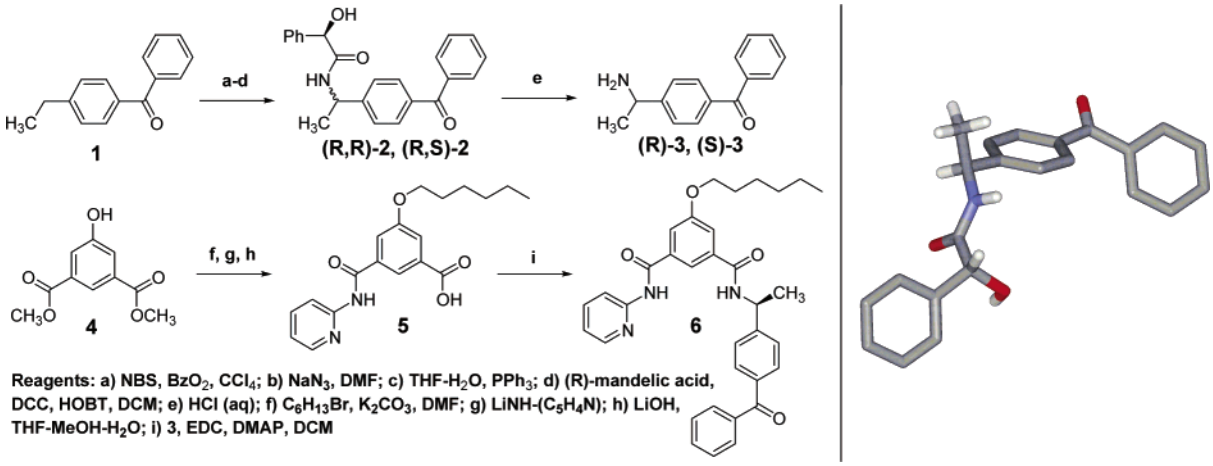
10.1021/jo020630e CCC: $25.00
Published on Web 11/20/2002

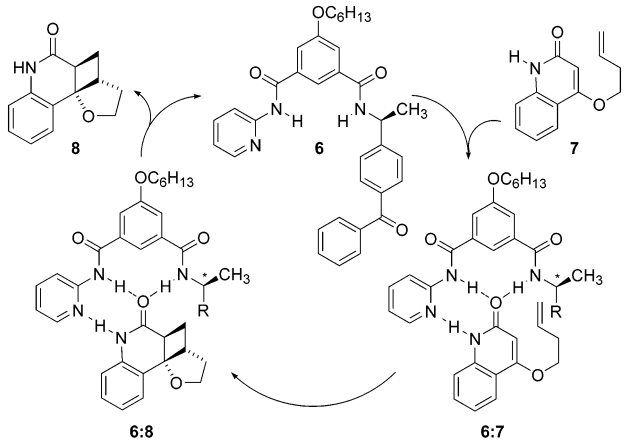
SCHEME 1. (Left) Synthesis of Chiral Photocatalyst 6; (Right) X-ray Crystal Structure of (*R*,*S*)-Mandelamide 2



guest complexes,[8] the "loose" asymmetric environment of chiral solvents and liquid crystals confers low levels of enantioselection.

Methods for *substoichiometric* chirality transfer have met with limited success. The use of circularly polarized lasers, i.e., so-called absolute asymmetric synthesis, gives disappointing enantiomeric enrichments.[14] Chiral photosensitizers provide modest enantiomeric enrichments for a limited range of substrates.[15] The asymmetric protonation of dienols generated via photodeconjugation of γ,γ-disubstituted enones or enoates in the presence of substoichiometric amounts of chiral amino alcohols proceeds with synthetically useful enantioinduction.[16] For this process, enantiodiscrimination does not occur in the excited state but in the tautomerization of the photochemically produced ground-state dienol.

SCHEME 2. Proposed Catalytic Cycle



Discussion

Design and Synthesis of Photocatalyst 6. As for any catalytic enantioselective process, a generally effective approach to the enantioselective catalysis of photomediated transformations in solution will require that (1) the substrate be placed in a well-defined chiral microenvironment upon binding to the template and (2) substrate-template binding confers a kinetic advantage to the transformation of interest. In principle, chiral molecular receptors that incorporate triplet-sensitizing residues meet these requirements.

With regard to the former requirement, the high levels of asymmetric induction observed for solution state photo[2 + 2]cycloadditions in synthetic host−guest systems strongly suggest that cycloaddition proceeds in a well-defined chiral microenvironment.[8] Here, hydrogen-bond formation dictates the orientation of the substrate with respect to the chiral receptor template in a distinct and predictable fashion. In general, the use of H-bond interactions as stereochemical control elements in photochemical cycloadditions is well precedented.[17]

The latter requirement is met through the incorporation of a triplet-sensitizing moiety. Here, the triplet lifetime of the sensitizer, in relation to the rates of diffusion and sensitization, defines a highly localized sphere of sensitization whereby energy transfer occurs via intermediacy of a triplet exciplex.[18] The stringent

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(14) For selected examples of enantioselective photochemistry via circularly polarized lasers, see: (a) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418. (b) Salam, A.; Meath, W. J. *J. Chem. Phys.* **1997**, *106*, 7865. (c) Salam, A.; Meath, W. J. *Chem. Phys. Lett.* **1997**, *277*, 199. (d) Shimizu, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1275. (e) Moradpour, A.; Kagan, H.; Baes, M.; Morren, G.; Martin, R. H. *Tetrahedron* **1975**, *31*, 2139.

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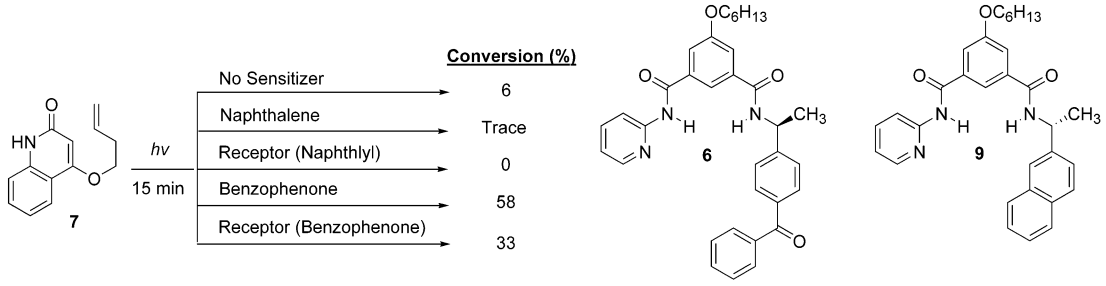
SCHEME 3. Irradiation of Quinolone 7 in the Presence and Absence of Selected Exogenous Chromophores[a]



[a] Conditions: [**7**] = 0.075 M, [additive] = 0.15 M. Irradiations were performed in $CDCl_3$ for 15 min using a medium-pressure Hg vapor lamp.

distance dependence of energy transfer is equivalent to a binding-induced rate enhancement, i.e., excitation of bound substrate should be favored over excitation of exogenous, untemplated substrate. If the lifetime of the exciplex is comparable to the rate of cyclization, exciplex formation can be enantiodiscriminating.

Predicated on this simple analysis, "sensitizing receptor" **6** is proposed. The binding motif embodied by **6** derives from structurally related carboxylic acid receptors.[19] The proposed substrate, 4-butenyloxy-2-quinolone **7**, embodies an identical array of H-bond donor−acceptor sites with respect to carboxylic acid guests and undergoes quantitative photo[2 + 2]cycloaddition, making it a suitable test substrate. A binding-induced rate enhancement is engineered by equipping receptor **6** with a triplet-sensitizing moiety in the form of a benzophenone residue. Although modeling of the host−guest complex indicates this first generation receptor **6** does not optimally obscure an enantiotopic π-face of the bound quinolone, exceptionally high levels enantiofacial bias are not necessary to illustrate proof of concept (vide supra).

The synthesis of receptor **6** is straightforward and involves the modular introduction of sensitizing and binding residues via amide bond formation. The sensitizing moiety, optically pure 4-(1-aminoethyl)-benzophenone **3**, is prepared from 4-ethyl-benzophenone **1** as outlined in Scheme 1. Resolution of racemic **3** is achieved through conversion to the (*R*)-mandelic acid amide, followed by chromatographic separation of the diastereomers and subsequent amide hydrolysis. Coupling of the resolved sensitizing amine fragment to the indicated monoamide monoacid **5** provides the sensitizing receptor **6** (Scheme 1).

Proposed Catalytic Mechanism: Receptor-Directed Energy Transfer. The proposed catalytic cycle is depicted in Scheme 2. Receptor **6** binds quinolone **7** to give the complex **6:7**. Energy transfer should be directed to the bound quinolone **7** owing to the distance dependence of energy transfer.[20] Thus, cycloaddition should occur in the chiral microenvironment of the **6:7** host−guest complex to yield optically enriched cycloadduct **8** in the form of the **6:8** complex. Finally, dissociation of cycloadduct **8** regenerates the uncomplexed receptor **6** to complete the cycle. Efficient templating of the cycloaddition will require the sensitized reaction to be fast relative to the unsensitized process. To suppress the background reaction of untemplated substrate, the substrate-product exchange equilibrium (**6:8** + **7** ⇆ **6:7** + **8**) should be fast, yet the cycloaddition of the templated substrate should be faster than the substrate off-rate (Scheme 2).

To establish the capability of receptor **6** to mediate energy transfer and to assess the sensitivity of the cycloaddition with respect to the presence of exogenous donor/acceptor chromophores, parallel experiments were conducted in which quinolone **7** was irradiated in the presence and absence of selected additives. Irradiation of **7** in the absence of an exogenous chromophore for 15 min results in 6% conversion. When **7** is irradiated in the presence of sensitizing (benzophenone, triplet energy = 69 kcal/mol) or quenching (naphthalene, triplet energy = 61 kcal/mol) chromophores, 58% conversion and trace conversion is observed, respectively.[21] Finally, when **7** is irradiated in the presence of sensitizing receptor **6** and quenching receptor **9**, which incorporate benzophenone and naphthalene residues, respectively, 33% and 0% conversions are observed. The expectation that sensitization and quenching efficiencies should be augmented in virtue of bringing the donor/acceptor chromophores together in the form of the **6:7** and **9:7** complexes is borne out for the irradiation performed in the presence of **9**. However, irradiation of quinolone **7** in the presence of sensitizing receptor **6** resulted in conversions lower than those observed in the irradiation of **7** in the presence of benzophenone (Scheme 3).

The fact that irradiation in the presence benzophenone induced higher levels of conversion than irradiation in the presence of sensitizing receptor **6** suggests the receptor scaffold contains a weakly quenching chromophore. Indeed, control experiments involving irradiation of quinolone **7** in the presence of structural subunits of receptor **6** reveal that the iso-phthaloyl moiety inhibits the cycloaddition (Scheme 4). *The presence of a weakly quenching chromophore in the receptor* ***6*** *scaffold proves to be advantageous as it provides an innocuous means of dissipating excitation energy when the receptor* ***6*** *binding site is unoccupied or nonproductively occupied by product*

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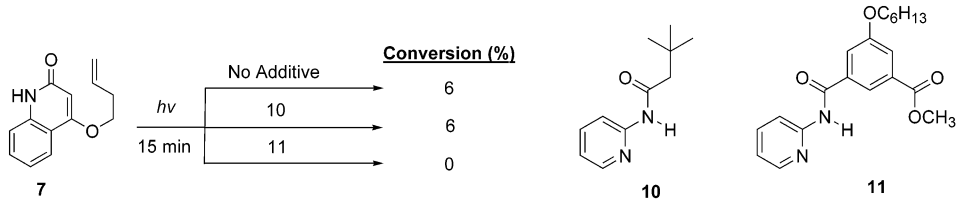
(21) See: Birks, J. *Photophysics of Aromatic Molecules*; John Wiley: New York, 1970.

SCHEME 4. Identification of Quenching Chromophore in the Receptor 6 Scaffold[a]



[a] Conditions: [**7**] = 0.075 M, [additive] = 0.15 M. Irradiations were performed in $CDCl_3$ for 15 min using a medium-pressure Hg vapor lamp.

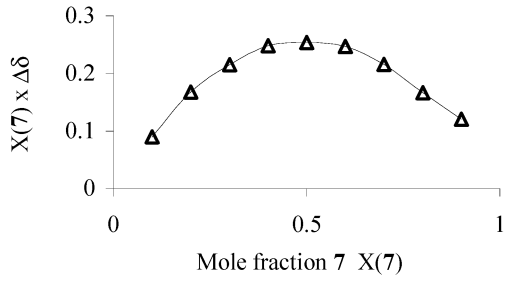


FIGURE 1. Stoichiometry determination.

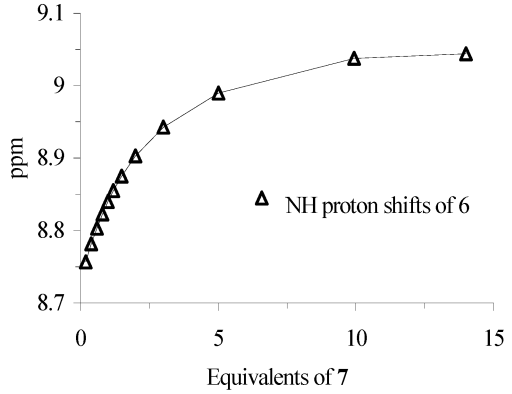
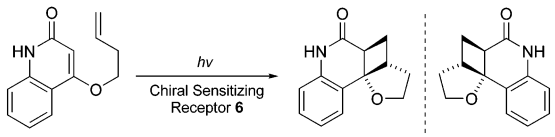


FIGURE 2. ^{1}H NMR titration plot.

***8**, i.e., energy is transferred to the iso-phthaloyl residue rather than to exogenous untemplated substrate, which would enhance the rate of the background reaction.*

Characterization of Host−Guest Binding Interactions. Confirmation of the anticipated 1:1 binding stoichiometry was obtained by applying Job's method of continuous variation to NMR results for species in rapid exchange (Figure 1).[22] An association constant for the formation of the **6:7** complex was determined via ^{1}H NMR titration experiments (log K_a = 2.5 ± 0.2 at 23 °C in $CDCl_3$) (Figure 2).[23] On the basis of the calculated K_a value, complex formation should be quantitative under the following concentration and stoichiometry: [**6**] = 0.15 M, [**7**] = 0.075 M. Within this concentration range, the dimeric association of quinolone **7** was undetectable via ^{1}H NMR titration in room-temperature $CDCl_3$.

TABLE 1. Photocycloaddition in the Presence of Variable Quantities of Photocatalyst 6[a]



entry	**10** (mol %)	temp (°C)	time (h)	conversion (%)[b]	ee (%)[c]
1	200	30	8	100	0
2	200	−20	12	100	8
3	200	−70	24	100	21
4	100	−70	30	100	22
5	50	−70	40	100	20
6	25	−70	70	100	19

[a] Conditions: [**7**] = 0.075 M, [additive] = 0.15 M. Irradiations were performed in $CDCl_3$ for 15 min using a medium-pressure Hg vapor lamp. [b] Reactions were periodically monitored by ^{1}H NMR, which enabled a determination of the percent conversion. The formation of byproducts was not observed by ^{1}H NMR. [c] Enantiomeric excess was determined by chiral stationary phase HPLC analysis using a Chiracel OD column.

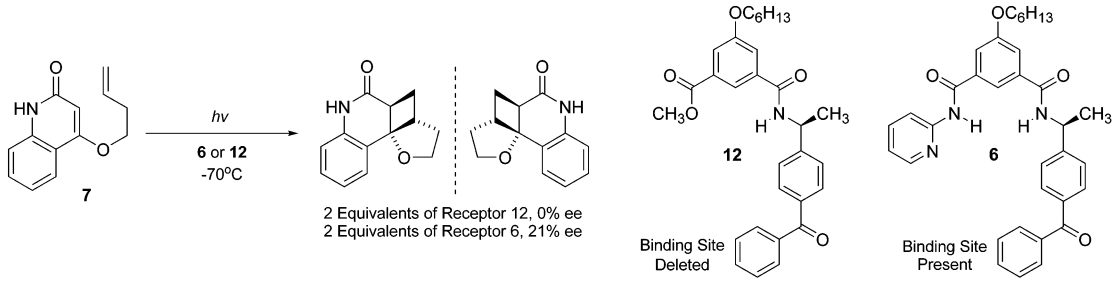
Enantioselective Catalytic Photocycloaddition. The stage was now set for proof-of-principle experiments. Irradiation of quinolone **7** in the presence of 2 equiv of sensitizing receptor **6** at ambient temperature gave quantitative conversion to **8** but without any detectable asymmetric induction (Table 1, entry 1). However, for reactions conducted at successively reduced temperatures, enantiodifferentiation became increasing apparent. Specifically, at −20 and −70 °C, quantitative conversion to **8** occurred in 8% and 21% enantiomeric excess, respectively. Notably, the time required for complete conversion of **8** increases as the rate of intermolecular exchange decreases in response to temperature. For a catalytic asymmetric process, the degree of asymmetric induction observed at −70 °C should persist upon successively reduced loadings of sensitizing receptor **6**. Indeed, reactions performed at −70 °C involving the use of equimolar quantities of sensitizing receptor **6** and quinolone **7** gave quantitative conversion to **8** with 21% enantiomeric excess. Similarly, for substoichiometric loadings of sensitizing receptor **6**, 0.5 equiv and 0.25 equiv, quantitative conversion to **8** occurred in 20% and 19% enantiomeric excess, respectively.

The persistence of the observed 20% enantiomeric excess across a range of receptor stoichiometries strongly suggests that the observed level of asymmetric induction results from the intrinsic enantiofacial bias conferred by

(22) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626.

(23) CHEM-EQUILI is a computer program for the calculation of equilibrium constant and related values from many types of experimental data (IR, NMR, UV−vis, and fluorescence spectrophotometry, potentiometry, calorimetry, conductometry, etc.). It is possible to use any combination of such kinds of methods simultaneously for reliable calculations of equilibrium constants. For a detailed description, see: (a) Solov'ev, V. P.; Vnuk, E. A.; Strakhova, N. N.; Raevsky, O. A. *Thermodynamic of Complexation of the Macrocyclic Polyethers with Salts of Alkali and Alkaline-Earth Metals*; VINTI: Moscow, 1991. (b) Solov'ev, V. P.; Baulin, V. W.; Strakhova, N. N.; Kazachenko, V. P.; Belsky, V. K.; Varnek, A. A.; Volkova, T. A.; Wipff, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1489.

SCHEME 5. Control Experiment Involving Irradiation of Quinolone 7 in the Presence of Receptor 6[a,b]



[a] Conditions: [**7**] = 0.075 M, [additive] = 0.15 M. Irradiations were performed in $CDCl_3$ for 15 min using a medium-pressure Hg vapor lamp. [b]Enantiomeric excess was determined by chiral stationary phase HPLC analysis using a Chiracel OD column.

the association of quinolone **7** to the sensitizing receptor **6**. To support this contention, a control experiment was performed. Irradiation of quinolone **7** was carried out under conditions identical to those described in Table 1 but in the presence of sensitizer **12** for which the binding site has been deleted. Quantitative conversion to cycloadduct **8** was observed, but without any detectable asymmetric induction. *Collectively, these and the aforementioned results establish substoichiometric chirality transfer from a receptor template to the prochiral substrate* (Scheme 5).

Conclusion and Outlook

While the use of transition metal templates in conjunction with chiral ligands has proven successful for myriad reaction types,[24] application of this approach to photochemical reactions is complicated by two factors: (1) most metals possess intense charge transfer bands in the spectral region of interest for organic photochemistry, and (2) photochemically promoted ligand loss is often a consequence of such absorptions, which disrupts the chiral microenvironment of the metal template at the crucial moment of bond formation. As supported by the collective results reported herein, a potentially general strategy for the enantioselective catalysis of photomediated transformations involves the use of molecular receptors equipped with appendant chiral sensitizing moieties. Future studies will focus on the development and optimization of receptor-sensitizer templates that confer heightened levels of enantiodiscrimination.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium−benzophenone ketyl prior to use. Dichloromethane was distilled from P_2O_5 when used as reaction media. All reactions were performed under Ar atmosphere unless otherwise noted. Literature procedures were used for the preparations of quinolone substrate **7**,[25] 4-ethylbenzophenone,[26] and 2-aminopyridine derivative **10**.[27] Photocycloaddition product **8** was characterized by ^1H and ^{13}C NMR, and results were found to be consistent with those reported in the literature.[23] Analytical TLC was performed on 0.25 mm silica gel 60-F plates and visualized under UV light. Flash chromatography was performed on silica gel 60 (200−400 mesh). ^1H NMR spectra were obtained at either 300 or 400 MHz, as indicated. ^{13}C NMR spectra were obtained at 75 MHz. Melting points were obtained in open capillaries and are uncorrected. Enantiomeric purity of sensitizing amines (*R*)-**3** and (*S*)-**3** was determined via chiral stationary phase HPLC.

4-(1-Bromoethyl)-benzophenone. 4-Ethylbenzophenone **1** (15.0 g, 71.36 mmol, 100 mol %) and *N*-bromosuccinimide (16.52 g, 92.81 mmol, 130 mol %) were combined in CCl_4 (350 mL). To this solution was added benzoyl peroxide (180 mg, 0.72 mmol, 1 mol %), and the reaction mixture was heated at reflux for 12 h. After reflux, the solution was cooled to 0 °C, and the solid precipitate was filtered. The filtrate was washed with 1 M aqueous Na_2CO_3, saturated aqueous NaS_2O_3, and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated, and the residue was purified via column chromatography (SiO_2, 0 → 2.5% ethyl acetate−hexane) to provide 4-(1-bromoethyl)-benzophenone as a red oil (15.4 g, 53.3 mmol) in 74% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (d, J = 7.2 Hz, 3H), 5.21 (q, J = 6.8 Hz, 1H), 7.43−7.58 (m, 5H), 7.74−7.78 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.80, 48.19, 76.68, 70.00, 77.31, 126.28, 127.81, 129.45, 129.94, 132.00, 136.74, 136.76, 146.77. HRMS: calcd [M + 1] for $C_{15}H_{13}OBr$, 289.0228; found, 289.0233. FTIR (film): 3019, 2400, 1659, 1608, 1278, 1216, 762, 702, 669, 420 cm^{-1}.

4-(1-Azidoethyl)-benzophenone. To a solution of 4-(1-bromoethyl)-benzophenone (14.24 g, 49.24 mmol, 100 mol %) in DMF (100 mL) was added NaN_3 (9.6 g, 147.7 mmol, 300 mol %). The reaction mixture was stirred at ambient temperature for 11 h and then partitioned between H_2O and Et_2O. The aqueous layer was washed with Et_2O, and the combined organic fractions were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the title compound as a yellow oil (11.9 g, 47.4 mmol) in 96% yield. The title compound was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, J = 6.8 Hz, 3H), 4.67 (q, J = 6.8 Hz, 1H), 7.39−7.45 (m, 4H), 7.51−7.55 (m, 1H), 7.74−7.79 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.80, 60.49, 76.67, 77.00, 77.32, 125.66, 127.72, 129.36, 129.93, 131.88, 136.55, 136.73, 144.71. HRMS: calcd [M + 1] for $C_{15}H_{13}N_3O$, 252.1137; found, 252.1130. FTIR (film): 3059, 2979, 2113, 1662, 1609, 1447, 1412, 1279, 1061, 939, 703, 436 cm^{-1}.

4-(1-Aminoethyl)-benzophenone. To a solution of 4-(1-azidoethyl)-benzophenone (11.9 g, 47.36 mmol, 100 mol %) in THF (400 mL) and H_2O (2.5 mL, 142.06 mmol, 300 mol %) was added triphenylphosphine (18.63 g, 71.03 mmol, 150 mol %). The reaction mixture was heated at reflux for 20 h and then concentrated to 20% volume. The reaction mixture was partitioned between H_2O and Et_2O, and the organic phase extracted with three portions of 1 M aqueous HCl. The combined aqueous washes were neutralized with 2 M aqueous NaOH and extracted three times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and then evaporated onto silica gel. Column chromatography (SiO_2, 0 → 10% methanol−dichloromethane) afforded 4-(1-amino-

(24) For an authoritative account, see: *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999.
(25) Kaneko, C.; Suzuki, T.; Sato, M.; Naito, T. *Chem. Pharm. Bull.* **1987**, *35*, 112.
(26) Bachmann, W. E.; Carlson, E., Jr.; Moran, J. C. *J. Org. Chem.* **1948**, *13*, 916.
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ethyl)-benzophenone as a yellow oil (7.92 g, 35.2 mmol) in 74.2% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (d, J = 6.6 Hz, 3H), 1.94 (s, 2H), 4.31 (q, J = 6.6 Hz, 1H), 7.55−7.61 (m, 4H), 7.66−7.72 (m, 1H), 7.88−7.93 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.31, 50.81, 76.57, 77.00, 77.42, 125.38, 127.92, 129.61, 130.11, 131.97, 135.77, 137.43, 152.24, 195.97. HRMS: calcd [M + 1] for $C_{15}H_{15}NO$, 226.1227; found, 226.1232. FTIR (film): 3370, 3299, 3058, 2965, 2249, 1658, 1607, 1447, 1280, 939, 852, 734, 443 cm^{-1}.

Derivatization of 4-(1-Aminoethyl)-benzophenone as (*R*)-Mandelic Acid Amide Diastereomers (*R*,*R*)-2 and (*R*,*S*)-2. To a 0 °C solution of 4-(1-aminoethyl)-benzophenone (11.88 g, 52.7 mmol, 100 mol %) and (*R*)-mandelic acid (8.83 g, 58 mmol, 110 mol %) in DCM (250 mL) was added DCC (11.97 g, 58 mmol, 110 mol %) and HOBT (710 mg, 5.3 mmol, 10 mol %). The reaction was allowed to stir for 14 h, during which time it was allowed to reach ambient temperature. The reaction mixture was filtered, and the filtrate was washed with first 1 M aqueous Na_2CO_3, 1 M aqueous H_2SO_4, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified via column chromatography (SiO_2, 20% → 40% ethyl acetate−hexane) to yield the upper R_f (*R*,*R*) diastereomer (7.4 g, 20.6 mmol) in 78% yield and the lower R_f (*R*,*S*) diastereomer (8.2 g, 22.8 mmol) in 87% yield as white solids. **Data for (*R*,*R*)-2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, J = 6.8 Hz, 3H), 4.55 (d, J = 4.1 Hz, 1H), 4.87 (d, J = 4.5 Hz, 1H), 5.00 (qt, J = 7.2 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 7.20−7.31 (m, 6H), 7.39−7.43 (m, 2H), 7.51−7.56 (m, 1H), 7.61−7.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.20, 48.66, 73.84, 76.69, 77.00, 77.31, 125.39, 126.15, 127.81, 127.89, 128.11, 129.50, 129.94, 132.04, 135.83, 136.80, 138.95, 147.26, 171.02, 195.60. HRMS: calcd [M + 1] for $C_{23}H_{21}NO_3$: 360.1600; found 360.1598. FTIR (film): 3400, 3018, 2401, 1655, 1518, 1279, 1216, 771, 443 cm^{-1}. Mp: 123−124 °C. $[\alpha]^{22}_D = -3.9°$ (*c* 1, $CHCl_3$). **Data for (*R*,*S*)-2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, J = 6.8 Hz, 3H), 4.43 (d, J = 3.8 Hz, 1H), 4.96 (d, J = 3.4 Hz, 1H), 5.05 (qt, J = 7.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.22−7.30 (m, 6H), 7.40−7.43 (m, 2H), 7.52−7.56 (m, 1H), 7.62−7.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.07, 49.54, 74.08, 76.68, 77.00, 77.31, 125.38, 126.18, 127.81, 127.93, 128.14, 129.50, 130.00, 132.02, 135.86, 136.83, 138.95, 147.10, 170.96, 195.56. HRMS: calcd [M + 1] for $C_{23}H_{21}NO_3$, 360.1600; found, 360.1596; FTIR (film): 3400, 3018, 2401, 1655, 1518, 1279, 1216, 771, 443 cm^{-1}. Mp: 121−123 °C. $[\alpha]^{22}_D = -115.6°$ (*c* 1, $CHCl_3$).

4-[(1*R*)-Aminoethyl]-benzophenone (*R*)-3: Mandelamide (*R*,*R*)-**2** (1.0 g, 2.8 mmol, 100 mol %) was heated at reflux in 20 mL concentrated aqueous HCl for 14 h. The cooled solution was extracted with Et_2O, basified with 3 M aqueous NaOH and extracted again with Et_2O. The combined Et_2O layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified via silica gel chromatography (2% → 7% MeOH−DCM) to yield (*R*)-**3** as a clear oil (0.4 g, 1.78 mmol) in 64% yield and 99+% ee. $[\alpha]^{22}_D = 25.9°$ (*c* 1, $CHCl_3$).

4-[(1*S*)-Aminoethyl]-benzophenone (*S*)-3. Prepared as described for (*R*)-**3**. $[\alpha]^{22}_D = -24.9°$ (*c* 1, $CHCl_3$).

Dimethyl-5-hexyloxyisophthalate. To a DMF solution (150 mL, 0.42 M) of compound **4** (13.07 g, 62.18 mmol, 100 mol %) was added 1-bromo-hexane (9.82 g, 59.22 mmol, 105 mol %) and K_2CO_3 (9.82 g, 71.06 mmol, 114 mol %), and the mixture was heated at 65 °C for 14 h. The reaction mixture was partitioned between H_2O and Et_2O. The aqueous layer was separated and washed with Et_2O. Combined organic layers were washed with 1 M aqueous NaOH and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue purified via column chromatography (SiO_2, 10% ethyl acetate−hexane) to yield the title compound (16.84 g, 57.2 mmol) in 92% yield as a yellow oil, which crystallized upon standing. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.29−1.34 (m, 6H), 1.42−1.47 (quintet, 2H), 1.73−1.80 (quintet, J = 7.2 Hz, 2H), 3.91 (s, 6H), 4.01 (t, J = 6.7 Hz, 2H), 7.71 (s, 2H), 8.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.92, 22.50, 25.55, 28.96, 31.43, 52.25, 68.49, 119.68, 122.61, 131.56, 159.13, 166.08. HRMS: calcd [M + 1] for $C_{16}H_{22}O_5$, 295.1546; found, 295.1542. FTIR (film): 3054, 2986, 2685, 2305, 1716, 1673, 1628, 1421, 1363, 1265, 1161, 978, 896, 738, 704 cm^{-1}. Mp: 52−53 °C.

Methyl 5-Hexyloxy-*N*-pyridin-2-yl-isophthalamate. To a solution of 2-aminopyridine (1.98 g, 21.02 mmol, 100 mol %) in THF (125 mL, 0.17 M) at −78 °C was slowly added a solution of *n*-butyllithium in hexanes (13.14 mL, 1.6 M, 100 mol %). The solution was allowed to stir for 0.5 h and then transferred dropwise via cannula into a −78 °C THF solution (50 mL, 0.85 M) of dimethyl-5-hexyloxyisophthalate (12.37 g, 42.03 mmol, 200 mol %). The reactions mixture was allowed to stir for 3 h, at which point 150 mL of 1 M aqueous $NaHCO_3$ was carefully added. The reaction mixture was partitioned between Et_2O and H_2O, and the aqueous layer was extracted with Et_2O. The combined ethereal layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified via column chromatography (SiO_2, 0 → 40% ethyl acetate−hexane) to yield the title compound (5.9 g, 16.6 mmol) in 79% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89−0.93 (t, J = 7.1 Hz, 3H), 1.32−1.51 (m, 6H), 1.77−1.84 (quintet, J = 7.4 Hz, 2H), 4.04−4.08 (t, 6.8 Hz, 2H), 7.13−7.18 (t, J = 6.2 Hz, 1H), 7.76 (s, 1H), 7.84−7.89 (m, 2H), 8.21−8.23 (d, J = 5.4 Hz, 1H), 8.69−8.72 (d, J = 7.6 Hz, 1H), 9.05 (s, 1H), 11.54 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04, 22.61, 25.67, 29.12, 31.56, 68.54, 116.24, 119.02, 119.68, 120.07, 121.51, 132.26, 134.76, 140.27, 144.96, 152.16, 159.43, 165.29, 170.93. HRMS: calcd [M + 1] for $C_{20}H_{24}N_2O_4$, 357.1814; found, 357.1812; FTIR (film) 3054, 2986, 2955, 2873, 2306, 1724, 1683, 1595, 1578, 1518, 1434, 1302, 1265, 1046, 896, 747 cm^{-1}. Mp: 112−114 °C.

5-Hexyloxy-*N*-pyridin-2-yl-isophthalamic Acid 5. To a solution of methyl 5-hexyloxy-*N*-pyridin-2-yl-isophthalamate (510 mg, 1.43 mmol, 100 mol %) in 3:1:1 THF/CH_3OH/H_2O (7 mL, 0.2 M) was added LiOH monohydrate (90 mg, 2.15 mmol, 150 mol %). The reaction mixture was allowed to stir at room temperature for 14 h, at which point NH_4Cl (115 mg, 2.15 mmol, 150 mol %) was added. The solution was concentrated to dryness and subjected to silica gel chromatography (SiO_2, 0 → 7% CH_3OH−CH_2Cl_2) to yield the title compound (440 mg, 1.28 mmol) in 90% yield as an amorphous white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (t, J = 6.8, Hz, 3H), 1.26−1.37 (m, 4H), 1.39−1.40 (m, 2H), 1.68−1.75 (quintet, J = 7.5 Hz, 2H), 4.05−4.08 (t, 6.2 Hz, 2H), 7.11−7.14 (t, J = 5.5 Hz, 1H), 7.56 (s, 1H), 7.78−7.82 (m, 2H), 8.12 (s, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.35 (d, J = 3.8 Hz, 1H), 10.95 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.87, 22.07, 25.13, 28.53, 30.97, 38.67, 38.95, 39.23, 39.50, 39.78, 40.06, 40.34, 68.11, 114.85, 117.76, 118.33, 119.90, 121.28, 132.39, 135.81, 138.09, 147.92, 152.09, 158.63, 165.05, 166.62. HRMS: calcd [M + 1] for $C_{19}H_{22}N_2O_4$, 343.1658; found, 343.1661. FTIR (film) 3683, 3614, 3261, 3019, 2958, 2934, 2400, 1672, 1594, 1580, 1470, 1340, 1217, 1045, 929, 750, 669, 419 cm^{-1}. Mp: 204−206 °C.

Sensitizing Molecular Receptor 6. To a solution of acid **5** (1.0 g, 2.92 mmol, 100 mol %) and 4-[(1*S*)-aminoethyl)]-benzophenone (660 mg, 2.92 mmol, 100 mol %) in CH_2Cl_2 (15 mL) were added EDC (620 mg, 3.21 mmol, 110 mol %) and DMAP (36 mg, 0.292 mmol, 10 mol %). The reaction mixture was stirred at ambient temperature for 14 h, evaporated onto silica gel, and subjected to column chromatography (SiO_2, 15% → 40% ethyl acetate−hexane) to yield the title compound (1.06 g, 1.9 mmol) in 66% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 6.5 Hz, 3H), 1.26−1.37 (m, 6H), 1.47 (d, J = 6.8 Hz, 3H), 1.68 (qt, J = 6.8 Hz, 2H), 3.86 (t, J = 6.5 Hz, 1H), 5.28 (qt, J = 7.2 Hz, 1H), 6.89−6.92 (m, 1H), 7.24−7.39 (m, 4H), 7.47−7.67 (m, 9H), 7.98−7.07 (m, 2H), 8.21 (d, J = 8.2 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.42, 21.92, 22.89, 25.90, 29.29, 31.74, 49.61, 68.49, 76.68, 77.00, 77.31, 114.14, 116.22, 116.60, 117.07, 119.60, 125.15, 125.80, 126.87, 128.04, 128.14, 135.09, 135.85, 137.89, 142.44, 147.10, 150.81, 158.94, 164.52, 164.93. HRMS: calcd [M + 1] for

$C_{34}H_{36}N_3O_4$, 550.2706; found, 550.2726. FTIR (film) 3370, 3299, 3058, 2965, 2249, 2200, 1658, 1607, 1447, 1412, 1308, 1280, 924, 852, 734, 620, 443 cm^{-1}. Mp: 146−147 °C. $[\alpha]^{22}_D = +65.0°$ (*c* 1, $CHCl_3$).

Naphthyl Receptor 9. To a solution of acid **5** (1.0 g, 2.92 mmol, 100 mol %) and *R*-(+)-1-(2-naphthyl)ethylamine (850 mg, 3.21 mmol, 110 mol %) in CH_2Cl_2 (15 mL, 0.2 M) were added EDC (620 mg, 3.21 mmol, 110 mol %) and DMAP (360 mg, 0.292 mmol, 10 mol %). The reaction mixture was allowed to stir at ambient temperature for 14 h, at which point the reaction mixture was evaporated onto silica gel and subjected to column chromatography (SiO_2, 10% → 40% ethyl acetate−hexane to yield the title compound (0.99 g, 2.0 mmol) in 68% yield as a waxy white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 6.8 Hz, 3H), 1.26−1.45 (m, 6H), 1.65 (d, J = 7.2 Hz, 3H), 1.77 (qt, J = 7.2 Hz, 2H), 1.94 (s, 1H), 3.98 (t, J = 6.5 Hz, 1H), 5.45 (qt, J = 7.2 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 7.01−7.04 (m, 1H), 7.40−7.53 (m, 5H), 7.68−7.83 (m, 6H), 8.20 (d, J = 4.1 Hz, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.42, 21.92, 22.89, 25.90, 29.29, 31.74, 49.61, 68.49, 76.68, 77.00, 77.31, 114.14, 116.22, 116.60, 117.07, 119.60, 125.15, 125.80, 126.87, 128.04, 128.14, 135.09, 135.85, 137.89, 142.44, 147.10, 150.81, 158.94, 164.52, 164.93. HRMS: calcd [M + 1] for $C_{31}H_{33}N_3O_3$, 496.2600; found, 496.2607; FTIR (film) 3370, 3299, 3058, 2965, 2249, 2200, 1658, 1607, 1447, 1412, 1308, 1280, 924, 852, 734, 620, 443 cm^{-1}. Mp: 146−147 °C. $[\alpha]^{22}_D = -31.1°$ (*c* 0.67, $CHCl_3$).

Acknowledgment is made to the Robert A. Welch Foundation (F-1466), the NSF-CAREER program, the Herman Frasch Foundation (535-HF02), the NIH (RO1 GM65149-01), donors of the Petroleum Research Fund administered by the American Chemical Society (34974-G1), the Eli Lilly Faculty Grantee program, and Research Corporation Cottrell Scholar Award (CS0927) for partial support of this research.

Note Added after ASAP Posting. A revised Table of Contents graphics was posted on November 22, 2002.

Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) and crystallographic data for (*R*,*S*)-**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020630E