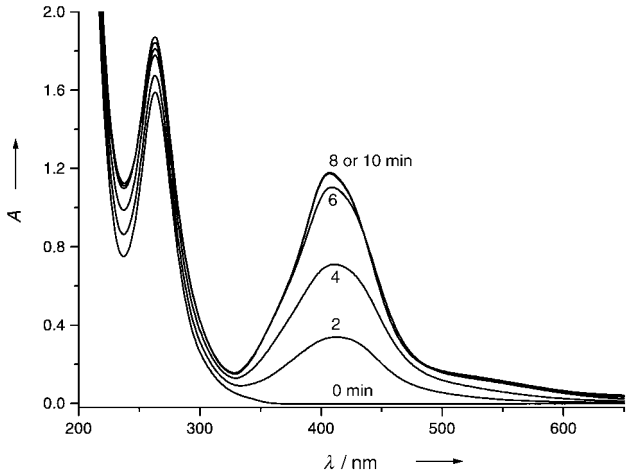

Figure 6. Photolysis profile: the formation of colloidal silver at different illumination times ($\lambda \approx 410$ nm) and the stability of $[SiW_{12}O_{40}]^{4-}$ photocatalyst ($\lambda = 263$ nm). Photolysis of a deaerated solution containing propan-2-ol (0.5 M), $[SiW_{12}O_{40}]^{4-}$ (0.035 mM), Ag^+ (0.1 mM) at pH 5 ($\lambda >$ 320 nm).

Experimental Section

$K_4[SiW_{12}O_{40}]$ was synthesized according to literature methods.[18] The metal ions added to the photolysed solution were aqueous solutions of $AgNO_3$, $PdCl_2$, $HAuCl_4$, or H_2PtCl_6.

In photolysis experiments, an aqueous solution of $SiW_{12}O_{40}^{4-}$ 0.7 mM and propan-2-ol 0.5 M, at pH 5, was put into a spectrophotometer cell (1 cm path length) deaerated with Ar and covered with a cerum cap. Photolysis was performed with a 1000 W Xe arc lamp, the light intensity of which was mechanically reduced by approximately 40%, while cut-off filters (up to 320 nm) were used to avoid direct photolysis of organic substrates. The absorption spectra of metal particles or catalyst were taken with a UV/Vis/NIR Spectrometer (Perkin Elmer Lambda 19), and the degree of reduction of POM in photolyzed, deaerated solutions was calculated from the known extinction coefficient of reduced catalyst, $SiW_{12}O_{40}^{5-}$, at 730 nm ($0.21 \times 10^4\ M^{-1}cm^{-1}$). TEM images were obtained using a Philips 200 kV microscope, and the samples were prepared by placing microdrops of colloid solution on a Formvar/carbon coated copper grid.

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Light-Controlled Nitric Oxide Generation from a Novel Self-Assembled Monolayer on a Gold Surface**

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Increasing evidence demonstrates that nitric oxide (NO) plays important roles in numerous physiological processes.[1–8] For instance, it is involved in the bioregulation of functions such as vasodilatation, neurotransmission, and hormone secretion in living bodies. In addition to these effects, NO has also been reported to act as efficient anticancer agent that inhibits key metabolic pathways to block the growth of or to kill cells.[9–13] This has stimulated intense interest in com-

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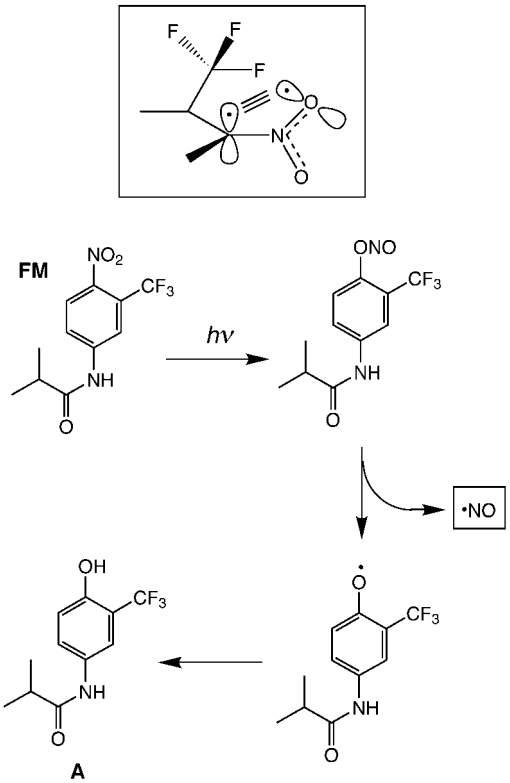
pounds which can deliver NO to a biological target on demand. In this regard, substances of low thermal reactivity that photochemically generate NO, preferentially with localized action, would be appealing photochemotherapeutic agents. Despite the considerable amount of reports on NO photogenerators in solution in the last years,[14–18] the delivery of quantitative amounts of NO at a desired target is still a critical problem for medical applications. A viable strategy for overcoming the site specificity dilemma would be the immobilization of suitable NO photogenerators on solid substrates. In this way, the probe can be driven directly to the area of interest and irradiated by using apposite fiber optic light guides. Such an approach is encouraged by the great variety of self-assembled monolayers (SAMs) of bioactive compounds on different metal electrodes. These systems are successfully applied in the biomedical field by using electrochemical stimuli.[19–24] Here we report on a novel SAM on a gold surface, which to the best of our knowledge is the first SAM that quantitatively releases NO exclusively by light excitation.

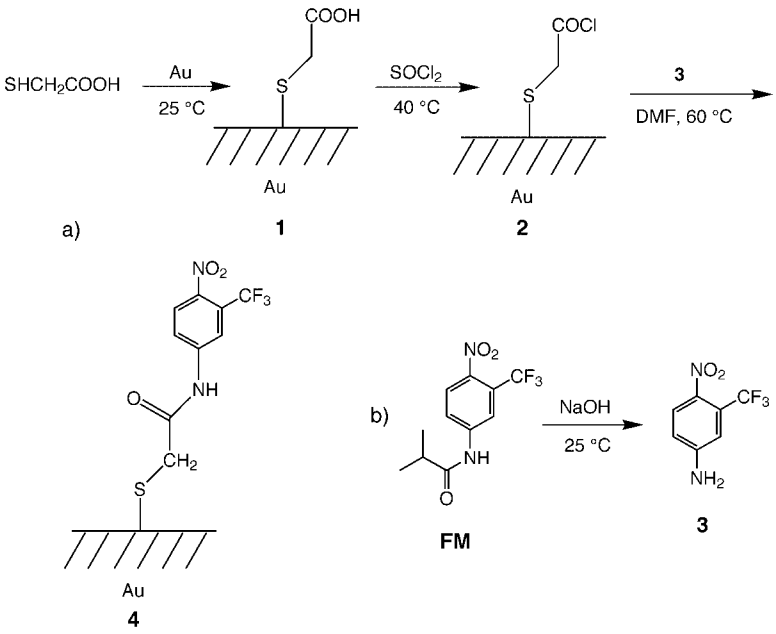
Our recent study on the photoreactivity of the anticancer drug flutamide (FM) was a decisive starting point for this work. We found that in homogeneous solution FM leads to the phenol derivative **A** as the sole stable photoproduct upon light excitation (Scheme 1).[25, 26] Owing to the presence of the CF_3 substituent the nitro group is almost perpendicular to the aromatic plane, with which it is therefore not conjugated. In this "out-of-plane" geometry, the p orbital of the oxygen atom has a constructive overlap with the adjacent p orbital of the aromatic ring in both the ground and excited states. Formation of **A** was rationalized on the basis of the well-known nitro-to-nitrite photorearrangement followed by rupture of the O–N bond to generate a phenoxy radical and NO (Scheme 1).



Scheme 1. Photodegradation of FM in homogeneous solution.

Besides contributing to the general picture of drug photochemistry, these findings stimulated the idea of developing a SAM of a FM-related compound on a gold surface and testing its ability to act as a NO photogenerator. In this regard, it is noteworthy that, apart from the low excitation energy required for NO production by FM photodecomposition (the absorption spectrum extends beyond 400 nm), the insignificant quantum yield of singlet oxygen by photosensitization[25] is an additional advantage in avoiding undesired side photoeffects.

The SAM **4** was prepared (Scheme 2) by first immobilizing sulfanylacetic acid on gold plates (1×1 cm, ca. 800 Å thick) by soaking (12 h at RT) to give SAM **1**, which was heated in refluxing $SOCl_2$ for 3 h to give SAM **2**. X-ray photoelectron spectroscopy (XPS) was used to check the degree of conversion after the reaction on the surface. The chlorine:



Scheme 2. a) Preparation of SAM **4**. b) Preparation of reagent **3**.

sulfur ratio in SAM **2** of 1:1.1 (±0.2) indicated quantitative conversion of **1** to **2**. Finally, SAM **4** was obtained by condensation of **2** with **3** (see Experimental Section for details) in anhydrous dimethylformamide for 12 h.

Again, the XPS analysis provided clear evidence that the reaction occurred efficiently: The signal of the sulfur 2p photoelectrons at 162 eV (binding energy) remained, whereas the signal of the chlorine 2p electrons (199 eV in **2**) completely disappeared and the diagnostically important and unambiguous signals related to fluorine 1s and nitrogen 1s electrons at 688 and 402 eV, respectively, appeared.

To test the suitability of **4** as an NO generator under light excitation, the monolayer-modified gold plate was immersed in phosphate buffer solution and irradiated. The NO photorelease was measured directly in real time with an NO electrode (see Experimental Section). Figure 1 shows that **4**

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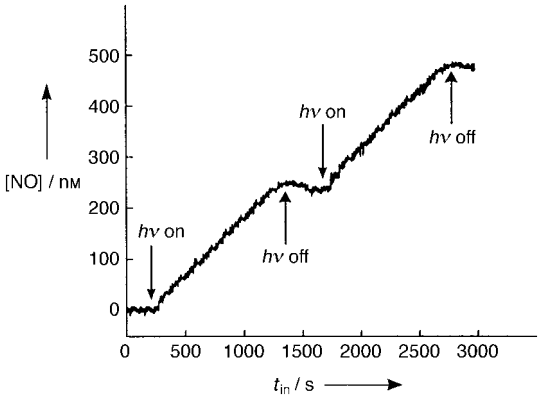
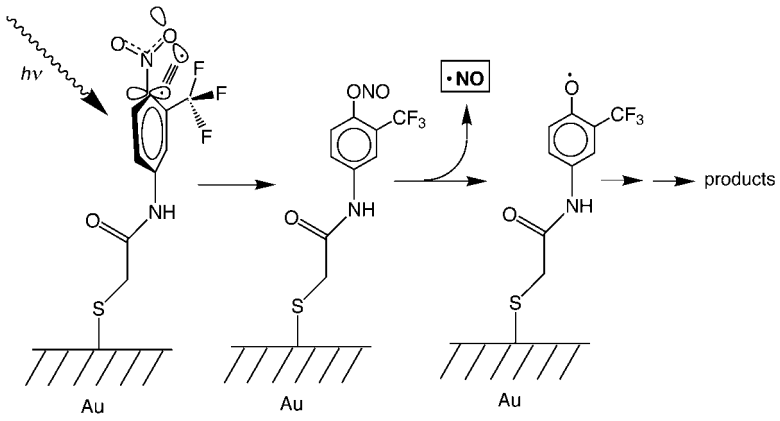


Figure 1. NO released upon photolysis ($\lambda_{exc} > 380$ nm) of SAM **4** immersed in phosphate buffer solution (3 mL, 10 mM, pH 7.4).

was stable to thermal release of NO, as indicated by the line with zero slope prior to irradiation. On excitation, slow and linear generation of NO at nanomolar levels was observed, which stopped when the light was turned off, after which a slight decline in the NO concentration was observed, most likely due to diffusion and oxidation by molecular oxygen in solution. The subsequent illumination of the sample triggered further NO photorelease from **4** until the light was turned off. The linearity observed in the performed experiments indicates that only a small fraction of SAM **4** is photodecomposed after about 50 min of irradiation under our experimental conditions.

On the basis of the electronic and molecular structure there are no reasons to believe that the photochemical behavior of SAM **4** differs from that of FM, and therefore a molecular mechanism for NO photogeneration triggered by the nitro-to-nitrite photorearrangement appears the most likely (Scheme 3).

In summary, the exclusive control of NO release through modulation of the illumination conditions, the relatively low excitation energy required, the absence of noxious side effects such as singlet-oxygen photosensitization, the thermal stability under physiological conditions, and the ease of preparation are remarkable advantages offered by SAM **4**. The coupling of such features with the ability to deliver light in discrete regions through optical fibers makes this compound an appealing candidate in the design of probes for applications where site-directed control of small and quantitative amounts of NO is required. This topic is currently under investigation in our laboratory.



Scheme 3. Proposed mechanism for the NO photogeneration from SAM **4**.

Experimental Section

3 was prepared as shown in Scheme 2b. After the hydrolysis reaction, **3** was purified on a silica gel column (40–63 μm; 1.0 × 20 cm) with dichloromethane:cyclohexane (3:2) as eluent and fully characterized by NMR spectroscopy and mass spectrometry. ^{1}H NMR ($CDCl_3$): $\delta = 4.46$ (br s, 2H, NH_2), 6.78 (dd, J(H6,H5) = 8.8, J(H6,H2) = 2.6 Hz, 1H, H6), 6.98 (d, J(H2,H6) = 2.6 Hz, 1H, H2), 7.97 ppm (d, J(H5,H6) = 8.8 Hz, 1H, H5). ^{19}F NMR ($CDCl_3$): $\delta = 16.34$ ppm (s, CF_3). FAB-MS (+; glycerol as matrix): m/z: 207 $[M+H]^+$. EI-MS (70 eV, 60 °C): m/z (%): 206 $[M]^{\bullet+}$ (25.5), 176 $[M-NO]^{\bullet+}$ (28.9), 167 (18.9), 160 $[M-NO_2^{\bullet}]^+$ (21.1), 125 $[176-CHF_2^{\bullet}]^+$ (20.0), 69 $[CF_3]^+$ (100).

4 was irradiated in a quartz fluorescence cuvette (10 mm pathlength) by using a Rayonet photochemical reactor equipped with eight RPR lamps with an emission in the 380–480 nm range with a maximum at 420 nm. The incident photon flux on the sample was about 5×10^{16} quanta per second.

NO photogenerated by **4** was measured with an amperometric sensor (ISO-NO, World Precision Instruments, Sarasota, FL), equipped with a data-acquisition system, and based on direct electrochemical detection of NO with short response time (< 5 s) and extremely low detection limit (1 nM). The sensor was accurately calibrated by mixing standard solutions of $NaNO_2$ with 0.1M H_2SO_4 and 0.1M KI according to the reaction[27] $4H^+ + 2I^- + 2NO_2^- \rightarrow 2H_2O + 2NO + I_2$.

XPS spectra were obtained on an AXIS HS machine (Kratos Analytical) with $Mg_{K\alpha}$ excitation (1253.6 eV). The binding energies of the collected spectra were calibrated against the Au 4f photoelectron signal originating from the underlying substrate.

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Complete Stereospecific Cyclopropanation of α,β-Unsaturated Amides Promoted by Sm/CH_2I_2**

José M. Concellón,* Humberto Rodríguez-Solla, and Cecilia Gómez

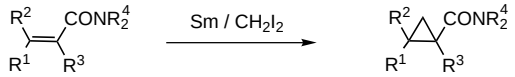
The cyclopropane ring is present in a great number of natural products.[1] In addition, the use of cyclopropanes in mechanistic studies[2] and their utility as synthetic intermediates[3] warrants the interest in these carbocycles from various fields in organic chemistry. The majority of the methodologies developed for the synthesis of cyclopropanes[4] rely on variants of the following reactions: Simmons–Smith cyclopropanation,[5] transition-metal catalyzed cyclopropanation of alkenes with diazomethane[6] or diazoesters,[7] and cyclopropanation of Michael acceptors.[8] However, these methods leave much to be desired: total control of diastereoselectivity in the synthesis of polysubstituted cyclopropanes is beyond reach, some methodologies call for toxic reagents, and in other cases, synthesis of cyclopropanes from unsaturated compounds in which the C=C bond is tri- or tetrasubstituted cannot be carried out.[9]

In particular, and to the best of our knowledge, the cyclopropanation of α,β-unsaturated amides in which the C–C double bond is tri- or tetrasubstituted has not been published. Only the transformation of mono- or disubstituted α,β-unsaturated amides into the corresponding cyclopropanecarboxamides has been described.[10] Consequently new methods for the diastereoselective construction of cyclopropylamides, in which the cyclopropane ring is polysubstituted, are of significant interest.

In their work on the synthetic applications of samarium(II) compounds Molander et al. reported the use of samarium amalgam/diiodomethane to cyclopropanate allylic alcohols with complete stereospecificity with respect to the olefin geometry.[11] Imamoto et al. described the cyclopropanation of lithium enolates derived from ketones by using SmI_2/CH_2I_2.[12] However, to the best of our knowledge, no cyclopropanation of α,β-unsaturated acid derivatives by using Sm/CH_2I_2 has been published.[13]

Recently, we described the SmI_2-promoted highly diastereoselective synthesis of vinyl halides,[14] α,β-unsaturated esters[15] and amides,[16] deuterated β,γ-unsaturated esters,[17] and vinylsilanes.[18] Here we report a new methodology for complete stereospecific cyclopropanation of α,β-unsaturated amides by using samarium and diiodomethane. The stereospecific synthesis of cyclopropylcarboxamides, in which the cyclopropane ring is di-, tri-, or tetrasubstituted, is achieved in high yield.

Treatment of several α,β-unsaturated amides **1** with samarium metal and diiodomethane at room temperature gave, after hydrolysis, the corresponding cyclopropylamides **2**, with complete stereospecificity and in high yield (Eq. (1), Table 1).



1 **2** (1)

These results show that this cyclopropanation reaction: a) takes place in high yield; b) is general and can be carried out starting from aliphatic (linear, branched, or cyclic) or aromatic α,β-unsaturated amides; c) is unaffected by the presence of bulky groups R^3 on the carbonyl amide (entries 3, 10, and 11); d) can be carried out starting from α,β-unsaturated amides **1**, in which the C=C bond is di-, tri-, or tetrasubstituted; e) takes place with complete stereospecificity—*trans*- and *cis*-cyclopropanamides are obtained from (*E*)- and (*Z*)-α,β-unsaturated amides, respectively (entries 1, 2 and 10, 11); f) takes place with very high chemoselectivity—selective cyclopropanation of the C=C bond conjugated with the carbonyl group is achieved in polyunsaturated amides (entry 5).[19]

The diastereoisomeric purity of compounds **2** was determined on the crude reaction products by ^1H NMR spectroscopy (300 MHz) and GC-MS, which showed the presence of a

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