1.74 (ddd, J = 12.3, 12.3, 9.5 Hz, 1 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.086 (s, 3 H).

4-*O*-Acetyl-3-*O*-(3-*O*-benzyl-2,6-dideoxy-4-*O*-methyl-α-D-*lyxo*-pyranosyl)-2,6-dideoxy-D-*lyxo*-pyranose (4c). A solution of **4b** (40 mg, 0.075 mmol) and $Et_3NH^+F^-$ (8 equiv) in CH_3CN (2 mL) was heated to 70 °C for 2.5 h. Saturated $NaHCO_3$ solution (0.5 mL) was added and the mixture was stirred at 23 °C for 10 min. The solution was diluted with additional aqueous $NaHCO_3$ (10 mL) and was extracted with EtOAc (4 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$ solution (20 mL) and brine (2 × 20 mL) and dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified with preparative TLC (0.5-mm plate, 50% EtOAc/hexanes, two elutions), giving 32 mg (100%) of disaccharide **4c** as ca. 2:1 mixture in favor of α-OH anomer.

This reaction has been run with the purified α,α- and α,β-anomers of **4b**, or on mixtures of them; the yields have always been quantitative. It was noticed that the β-TBDMS anomer of **4b** was desilylated faster when a mixture was used. The following ^1H and ^{13}C NMR assignments are based on 2D NMR ^1H–^1H correlation, ^1H–^{13}C correlation, and ^1H decoupling experiments.

Data for **4c**: R_f 0.20 (50% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) data for α-OH anomer δ 7.40–7.25 (m, 5 H), 5.40 (d, J = 3.5 Hz [after D_2O exchange], 1 H, H_1), 5.14 (d, J = 2.6 Hz, 1 H, H_4), 5.12 (d, J = 3.8 Hz, 1 H, $H_{1'}$), 4.56 (s, 2 H), 4.23–4.17 (m, 2 H, H_3, H_5), 3.80–3.75 (m, 1 H, $H_{3'}$, overlapping with $H_{3'}$ and $H_{5'}$ of the β-anomer), 3.76 (q, J = 6.5 Hz, 1 H, $H_{5'}$), 3.58 (s, 3 H), 3.31 (br s, 1 H, $H_{4'}$), 2.85 (br s, 1 H, OH), 2.10 (s, 3 H), 2.02 (ddd, J = 12.5, 12.5, 3.8 Hz, 1 H, $H_{2'ax}$), 1.89 (ddd, J = 12.6, 12.6, 3.5 Hz, 1 H, H_{2ax}), 1.73 (br dd, J = 12.6, 4.9 Hz, 2 H, H_{2eq}, $H_{2'eq}$, almost superimposed), 1.22 (d, J = 6.5 Hz, 3 H, $H_{6'}$), 1.10 (d, J = 6.5 Hz, 3 H, H_6); data for β-OH anomer δ 7.40–7.25 (m 5 H), 5.08 (d, J = 3.6 Hz, 1 H, $H_{1'}$), 5.05 (d, J = 3.2 Hz, 1 H, H_4), 4.78 (ddd, J = 9.6, 6.6, 1.9 Hz, 1 H, H_1), 4.56 (s, 2 H), 4.25–4.17 (m, 1 H, H_5), 3.38 (ddd, J = 12.3, 4.8, 3.2 Hz, 1 H, H_3), 3.80–3.73 (m, 2 H, $H_{3'}$, $H_{5'}$), 3.58 (s, 3 H), 3.54 (d, J = 6.6 Hz, 1 H, OH), 3.31 (br s, 1 H, $H_{4'}$), 2.09 (s, 3 H), 2.05–1.68 (m, 4 H, H_{2ax}, $H_{2'ax}$, H_{2eq}, and $H_{2'eq}$), 1.22 (d, J = 6.5 Hz, 3 H, $H_{6'}$), 1.18 (d, J = 6.4 Hz, 3 H, H_6); ^{13}C NMR (125 MHz, $CDCl_3$) (for the mixture) δ 170.75 (carbonyl, for both anomers), 138.59, 138.49, 128.34, 128.32, 127.50, 127.45, 127.23, 127.21, 95.62, 94.99, 94.36, 92.37, 78.64, 78.54, 74.57, 74.40, 70.34, 70.11, 70.08, 69.42, 68.89, 67.50, 67.12, 66.98, 66.70, 64.72, 61.38, 61.36, 34.89, 31.42, 30.17, 30.06, 20.82, 20.77, 16.97 ($C_{6'}$ for both anomers), 16.78, 16.66; IR (neat) 3420, 3090, 3070, 2860, 2815, 1740 cm^{-1}; HRMS for $C_{22}H_{30}O_7$ ($M^+ - H_2O$), calcd 406.1991, found 406.1974. Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 61.96; H, 7.64.

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Registry No. 1, 6988-58-5; 2, 7059-24-7; 4a, 106023-24-9; α,α-4b, 131013-38-2; α,β-4b, 131013-40-6; β,β-4b, 131013-41-7; α-4c, 131041-37-7; β-4c, 131013-42-8; 8, 99603-55-1; 9, 127851-95-0; 10, 106062-13-9; 10 benzyl ether, 106062-14-0; 11, 106062-15-1; 11 TBDMS derivative, 131013-39-3; α-12, 107908-97-4; β-12, 131013-43-9; α-13, 131013-31-5; β-13, 131013-44-0; α-14, 4833-12-9; β-14, 106023-19-2; α-15, 106023-20-5; β-15, 106023-21-6; 16, 4092-40-4; 17, 3868-01-7; α-18, 106023-22-7; β-18, 106023-23-8; 19, 75810-18-3; 21, 131013-32-6; 22, 131013-33-7; α-23, 131013-34-8; β-23, 131013-45-1; α-24, 131013-35-9; β-24, 131013-46-2; 25, 131013-36-0; 26, 131100-33-9; α-27, 131041-38-8; β-27, 131013-47-3; α-28, 131013-37-1; β-28, 131013-48-4; 29, 85273-19-4; 30, 131100-34-0; 31, 131100-35-1.

Supplementary Material Available: Experimental procedures for the syntheses of 14α–19 and ^1H NMR spectra of 24 (α,β mixture), 25, 26, α,α-4b, β,α-4b, and β,β-4b (10 pages). Ordering information is given on any current masthead page.

Notes

Mechanistic Details for SET-Promoted Photoadditions of Amines to Conjugated Enones Arising from Studies of Aniline–Cyclohexenone Photoreactions

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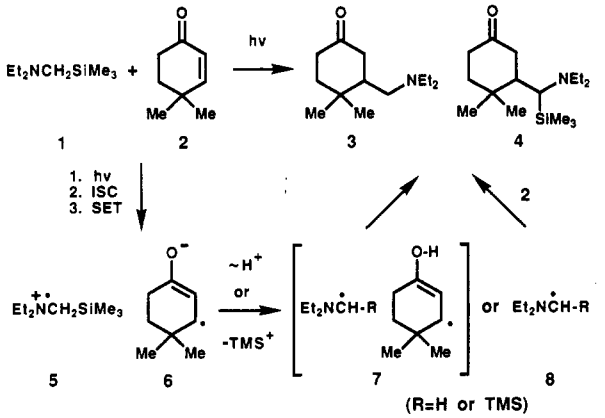
Introduction

Previous studies exploring photoaddition reactions of α-silyl amines and α,β-unsaturated ketones have led to a number of interesting proposals concerning the mechanistic features of these single electron transfer (SET) promoted processes[1,2] and have suggested potential synthetic applications.[3] In mechanistic studies of the *N*-[(trimethylsilyl)methyl]-*N*,*N*-diethylamine (1) addition to 4,4-dimethylcyclohex-2-en-1-one (2), we observed that the relative yields of the non-TMS (3) and TMS adducts (4)

Scheme I

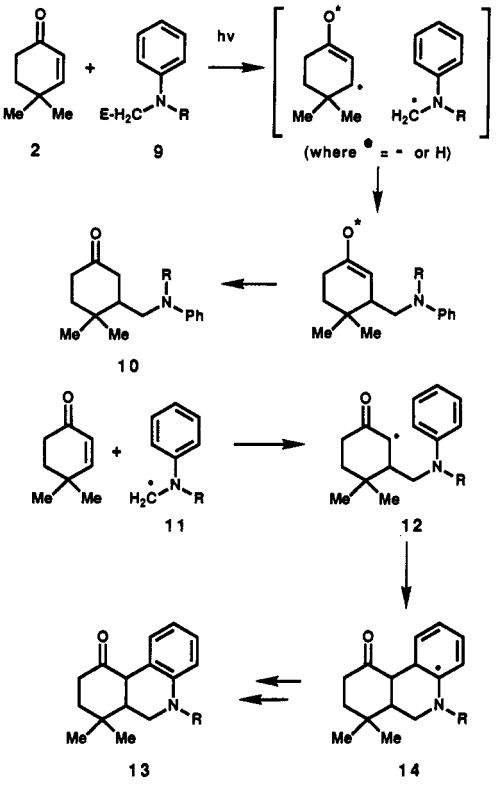


were dependent upon the nature of the solvent, metal cation additives, and amine concentration. These results were interpreted in terms of a mechanism (Scheme I) in which the relative rates of intermediate amine cation radical 5 deprotonation and desilylation are governed by the basicity of the enone anion radical 6, which itself is controlled by hydrogen bonding and metal cation coordination. Furthermore, we suggested that in cases where the enone anion radical is rendered nonbasic by hydrogen bonding in polar protic solvents, amine cation radical 5

(1) Yoon, U. C.; Kim, J. U.; Hasegawa, E.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109*, 4421.
(2) Hasegawa, E.; Xu, W.; Mariano, P. S.; Yoon, U. C.; Kim, J. U. *J. Am. Chem. Soc.* **1988**, *110*, 8099.
(3) Xu, W.; Jeon, Y. T.; Hasegawa, E.; Yoon, U. C.; Mariano, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 413.

0022-3263/91/1956-1655$02.50/0

Scheme II



deprotonation could still occur by ion radical pair dissociation followed by proton transfer from **5** to amine **1**.

On the basis of these results and those obtained from an investigation of the 9,10-dicyanoanthracene SET-sensitized addition of silyl amine **1** to enone **2**, we also proposed that under conditions which favor proton transfer in the contact ion radical pair, product formation would occur by radical coupling of the α-amino and hydroxyallyl radicals within the solvent cage **7** (R = TMS). Further, we suggested that when free α-amino radicals **8** (R = H or TMS) are formed by amine-promoted deprotonation or solvent-induced desilylation of free amine cation radicals **5**, adduct formation would occur by conjugate addition of the amino radicals to ground-state enone.

Observations made in our current studies of photoaddition reactions of *N,N*-dimethylaniline (**15**) and its silyl analogue **19** to cyclohexenone **2** have provided convincing evidence for the operation of two mechanistic pathways (radical addition and radical coupling) in amine–enone SET-promoted photoaddition reactions. In addition information pertinent to the detailed mechanistic nature of α-silyl amine photoadditions has emanated from these investigations.

The design of these efforts was based upon the following reasoning. Pathways for these processes involving in-cage coupling of an α-amino radical to an enone anion radical or its O-protonated counterpart results in generation of either an enolate anion or a neutral enol which can serve as direct precursors of the photoproducts. On the other hand, reactions via a conjugate radical addition route produces an α-keto radical, which then can undergo H-atom abstraction or sequential reduction–protonation to generate photoadducts. Unlike the enolate anion or enol intermediates, the electron-deficient α-keto radical can in theory react further with a properly disposed electron-rich radical trap. The trapping reaction would be facilitated by incorporation of an electron-rich π-moiety as part of either the starting enone or amine substrate. We anticipated that *N*-phenyl-substituted α-amino radicals **11** arising from aniline derivatives would be appropriate for this purpose since putative α-keto radical intermediates such as **12** (Scheme II) should be suitably configured to undergo a predictably efficient radical cyclization to produce stabilized tricyclic cyclohexadienyl radicals **14**. On this basis, we proposed that SET reactions of anilines **9** with the cyclohexenone **2**, which occur by radical coupling pathways, would yield simple adducts **10** while those that follow radical addition mechanisms would produce tricyclic adducts **13**. Of course, it is also possible for the radical addition route to generate simple monocyclic adducts like **10** if radical cyclization is slow relative to H-atom abstraction from solvent or sequential reduction–protonation.

Table I. Medium Effects on the Monocyclic/Tricyclic Adduct Ratio (16:17) and on the TMS/Non-TMS Adduct Ratio (20:16) in Respective Photoadditions of *N,N*-Dimethylaniline (15) and *N*-[(Trimethylsilyl)methyl]-*N*-methylaniline (19) to 4,4-Dimethylcyclohex-2-en-1-one (2)

medium[a]	16:17 ratio from reaction of 2 + 15[b]	20:16 ratio from reaction of 2 + 19[b]
MeCN	8	>29
25% H_2O–MeCN	0.2	0
MeOH	1.4	0
25% H_2O–MeOH	0.9	0
0.1 M $LiClO_4$–MeCN	2	>26
0.25 M $LiClO_4$–MeCN	1	12
0.4 M $LiClO_4$–MeCN	0.3	3

[a] Photoreactions were conducted on 1×10^{-2} M solutions of both **2** and **15** to ca. 11–60% conversion. [b] Product ratios were determined by HPLC analysis on a reverse-phase (C-18) column with 20% H_2O–MeOH as eluant.

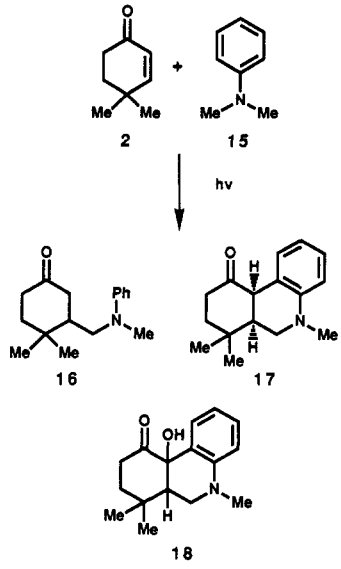
The predictions embodied in the above proposal have served as the foundation for our current experimental studies. These efforts have demonstrated that for photoadditions of α-silyl amines to enones occurring in protic solvents, intermediate amine cation radicals undergo rapid desilylation to generate solvent-caged radical pairs, which yield adducts by a radical coupling mechanism. In contrast, cation radicals arising by SET from non-silicon-containing anilines to enone excited states in protic solvents undergo deprotonation to produce free α-amino radicals, which then are transformed to adducts by radical addition pathways.

Results

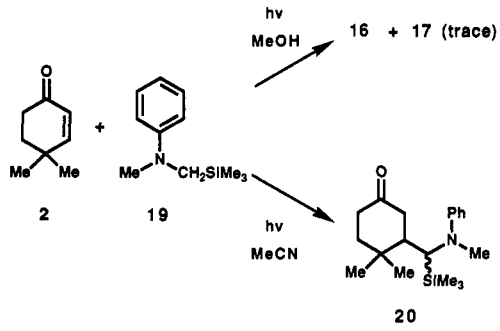
Photoadditions of Anilines 15 and 19 to Cyclohexenone 2. Preparative, direct irradiation (λ > 320 nm) reactions of cyclohexenone **2** with *N,N*-dimethylaniline (**15**) and with *N*-[(trimethylsilyl)methyl]-*N*-methylaniline (**19**) were conducted by using 1×10^{-2} M solutions of the enone and amines in a variety of solvent systems (see Table I). Photoreaction of **2** and **15** in MeOH produced two products,[4] characterized as the monocyclic adduct **16** (14%) and tricyclic adduct **17** (10%) (Scheme III). In addition, a trace quantity of the tricyclic keto alcohol **18** was also produced in this process, presumably by secondary oxidation of **17** during workup of the photolysate and/or product separation. The structures of **16** and **17** and the stereochemistry of **17** were determined by use of spectroscopic data and comparisons of these data with those accumulated for closely related photoproducts (e.g., **3** and **4**) prepared in our earlier studies[1,2] and for analogous

(4) The tricyclic hydroxy ketone **18** detected following workup and separation of the photolysate most probably arises by oxidation of the primary tricyclic ketone photoproduct **17**. This secondary oxidation is not surprising for a substance like **17**, which contains a benzylic ketone function and a basic tertiary amine site.

Scheme III



Scheme IV



carbocyclic hydrophenanthrenones prepared and characterized earlier by Thompson and Long.[5]

The effects of solvent and additives on the photoreaction of enone **2** with aniline **15** were explored. The data (Table I) from these experiments indicate that the ratio of monocyclic to tricyclic adducts, **16**:**17**, varies greatly as the protic nature of the medium is changed. Accordingly, photoaddition in MeCN gives the monocyclic adduct (**16**:**17** > 8) nearly exclusively while reaction in H_2O–MeCN mixtures, in MeOH, or in MeCN containing high concentrations of $LiClO_4$ leads to the tricyclic adduct predominantly.

In contrast, direct irradiation photoadditions of the (silymethyl)aniline **19** with enone **2** produced, at most, only trace quantities of the tricyclic adduct **17** under all conditions. Thus, irradiation of 1×10^{-2} M solutions of both **19** and **2** in MeOH led to formation of the monocyclic adduct **16** in reasonably high yield (64%) along with a trace (<1%) quantity of **17** (Scheme IV). Photoaddition of **19** to **2** in MeCN under otherwise identical conditions resulted in exclusive generation of an ca. 1:1 mixture of the diastereomeric silicon-containing monocyclic adducts **20** (29%). Identification of **20** was made possible by comparisons of key spectroscopic data for the inseparable mixture of stereoisomers with those previously recorded[1,2] for the closely related silicon-containing adducts **4**. Consistent with the results of our earlier efforts,[1,2] the ratio of the TMS and non-TMS monocyclic adducts, **20**:**16**, arising from photoreaction of **19** with **2** was dependent upon the nature of the photoreaction medium. For example, the non-TMS adduct **16** predominates in protic media (e.g., MeOH or 25% H_2O–MeCN) while the TMS adduct **20** is formed exclusively in the nonprotic MeCN. Moreover, Li cation effects noted earlier in studies of the addition of silyl amine **1** to enone **2** are seen again in reaction of silyl aniline **19** to this same ketone. Accordingly, varying the $LiClO_4$ concentration from 0.1 M to 0.4 M in MeCN causes the **20**:**16** ratio to decrease from >26 to 3.

The final experiments performed in the current investigation involved the 9,10-dicyanoanthracene (DCA) SET-photosensitized addition of (silylmethyl)aniline **19** to cyclohexenone **2**. Our goal was to determine the ratio of monocyclic (**16**) and tricyclic (**17**) adducts formed in a process in which an α-amino radical intermediate, produced by SET to the singlet excited state of DCA[1,2,7] followed by desilylation, reacts with the enone by a conjugate addition mechanism exclusively. A difficulty in selectively executing the DCA-sensitized reaction arises from the facts that low DCA concentrations are required in order to prevent secondary oxidation of the intermediate α-amino radical[6] and that high concentrations of the cyclohexenone **2** are needed to efficiently trap this same radical. Under our preparative photochemical conditions, it is difficult to meet both criteria and simultaneously prevent light absorption by—and thus direct irradiation of—enone **2**. Consequently, SET-photosensitized reactions were performed by irradiation ($\lambda > 320$ nm) of 6×10^{-6} M solutions of DCA in 20% MeCN–MeOH containing 2.0 M (silylmethyl)aniline **19** and varying (0.2 to 0.01 M) concentrations of cyclohexenone **2**. HPLC analyses of the photolysates formed in these processes showed that the **16**:**17** ratio varied with enone concentration in the following manner: **16**:**17** vs [**2**]; 12 at 0.2 M, 7 at 0.1 M, and 0.4 at 0.01 M. These results suggest that in the DCA-sensitized reaction, where only the radical addition mechanism is possible, the tricyclic adduct **17** is produced either predominantly or exclusively.

Discussion

Origin of the Tricyclic Photoadduct. As discussed in the Introduction, the only reasonable mechanistic pathway for formation of the tricyclic adduct **17** in the respective photoadditions of anilines **15** and **19** to cyclohexenone **2** involves a tandem conjugate addition–radical cyclization sequence (Scheme II). This route gives the aminocyclohexadienyl radical intermediate related to **14**. Transformation of this species to tricyclic adduct **17** presumably involves H-atom abstraction from solvent or the anion radical of **2** followed by oxidation of the resulting aminocyclohexadiene during workup of the photolysate. The radical cyclization step in this sequence, although being 6-endo in nature, should be quite favorable owing to the fact that the α-keto radical is electron deficient and the internal amino-substituted arene moiety is electron rich. Substituent controls via FMO effects of radical addition processes is now well-known.[8] In addition, this

(5) Thompson, H. W.; Long, D. J. *J. Org. Chem.* **1988**, *53*, 4201. Characteristic stereochemical information for **17** comes from the observed ^{1}H NMR chemical shift of 3.80 ppm and coupling constant of 5.9 Hz for the α-keto, methine proton. In comparison, a carbocyclic analogue of **17**, lacking the *gem*-dimethyl groups and having a methylene group in place of the methylamino moiety, shows the corresponding proton as a doublet at 3.89 ppm and a coupling constant of 5.5 Hz. In contrast, the α-keto methine proton in the trans-fused carbocyclic analogue of **17** resonates at 3.68 ppm with a coupling constant of 11.2 Hz.

(6) We have noted in our earlier studies[3] that DCA with a reduction potential of −0.89 V is capable of rapidly oxidizing α-amino radicals that have oxidation potentials of ca. −1 V.

(7) Hasegawa, E.; Brumfield, M.; Yoon, U. C.; Mariano, P. S. *J. Org. Chem.* **1988**, *53*, 5435.

cyclization reaction should display a kinetic preference for formation of the cis-fused tricyclic radical as a result of a stereoelectronically favored axial attack at the α-keto radical center by an equatorially appended aniline-containing side chain.

The monocyclic adducts **16** and **20** formed in the respective photoadditions of anilines **15** and **19** to enone **2** in theory could arise by radical coupling and/or radical addition pathways. Thus, carbon–carbon bond formation between α-amino radicals and either protonated or charged enone anion radicals as part of solvent-caged pairs would lead to the direct precursors of these monocyclic adducts. Alternatively, α-keto radicals produced by conjugate α-amino radical addition to enones could partition to monocyclic adducts if H-atom abstraction is faster than cyclization. Results from the DCA SET-sensitized additions of **19** to **2** appear to suggest, however, that radical coupling is by far the major, if not exclusive, pathway for monocyclic adduct formation. In the DCA-sensitized process, α-amino radical intermediates are generated by a route involving SET from (silylmethyl)aniline **19** to the DCA singlet excited state.[2,3,7] By use of this methodology, the enone excited state is avoided and, as a result, the corresponding enone anion radical is not formed. Thus, the radical conjugate addition mechanism is the only one available for adduct formation in the DCA-sensitized process. The near exclusive production of tricyclic adduct **17** under these conditions (i.e., at low [**2**]) strongly suggests that the α-keto radical formed by addition of the α-amino radical to the enone undergoes preferential cyclization to form the tricyclic adduct **17** rather than H-atom abstraction to yield monocyclic adduct **16**.

Detailed Mechanisms for Amine–Enone SET Photoadditions. It follows from the discussion presented above that the nature of the adducts produced in the SET photoadditions of anilines **15** and **19** to cyclohexenone **2** is an indicator of the mechanistic pathway followed. Specifically, tricyclic adduct **17** derives from a conjugate radical addition route while the monocyclic products **16** and **20** arise via radical pair coupling pathways. With these conclusions in mind, it is possible to interpret the results of these photoaddition reactions and, in particular, to understand how the nature of the amine substrate and photoreaction medium govern the detailed mechanistic pathways followed.

In photoadditions of *N*,*N*-dimethylaniline (**15**) to cyclohexenone **2**, the tricyclic/monocyclic (**17**:**16**) product ratio varies significantly with changes in the reaction medium. In the nonprotic solvent, MeCN, and in the absence of hard metal salts ($LiClO_4$), the major product is the monocyclic adduct **16**. Thus, the major mechanistic route followed under these conditions is one in which adduct formation occurs by radical coupling. This result is consistent with earlier proposals[1,2,9] that in nonprotic solvents proton transfer occurs in an ion radical pair formed by SET from the amine to the enone triplet excited state. Intra-ion-pair proton transfer should generate a solvent-caged radical pair in which radical coupling could be more rapid than cage collapse to form free radical species.

In contrast, the radical addition mechanism becomes a more important contributor in the dimethylaniline–enone photoadditions occurring in protic solvents (e.g., MeOH, H_2O–MeCN) or in media containing high concentrations of the lithium cation. These observations are fully consistent with our earlier proposal[2] that deprotonation of amine cation radicals, formed by amine–enone photoinduced SET, involves a neutral amine rather than an enone anion radical as the base. The basicity of enone anion radicals[10] must be significantly diminished in these solvent systems owing to hydrogen bonding or lithium complexation at the electron-dense oxyanionic center.[10d] Moreover, the current results suggest that amine-promoted deprotonation of the amine cation radical occurs at a solvent-separated or free ion stage. The resulting free α-amino radical should have a higher probability (concentration determined) to react with the neutral enone rather than a free solvated enone anion radical. Clearly, the radical addition mechanism leading to tricyclic adduct **17** becomes increasingly competitive in protic or Li^+-containing solvent systems because amine cation radical deprotonation under these conditions does not involve the enone anion radical as a base.

The results of our studies with the (silylmethyl)aniline **19** have provided important information about the amine cation radical desilylation process. Photoreaction of **19** with cyclohexenone **2** in MeOH forms the monocyclic adduct **16** in high yield. This observation demonstrates that the radical coupling mechanism is adhered to exclusively under these conditions presumably as a result of rapid, solvent-induced desilylation of silyl amine cation radical **21** in a contact ion radical pair. While kinetic studies have not yet been performed to determine the rates of silyl amine cation radical desilylation, investigations with related allyl- and benzylsilane cation radicals suggest that desilylation of the cation radicals derived from the hydrocarbon silane analogues occurs faster than diffusion from the solvent cage and produces caged radical pair intermediates.[11–13] The current results are consistent with these findings and suggest further that desilylation of the nitrogen-centered cation radicals is also a fast process responsible for the high yielding generation of solvent-caged, radical pair precursors of adducts.

One final aspect of our studies that requires attention concerns the observed medium effects on product distributions arising from irradiation of the cyclohexenone **2** in the presence of silyl amine **19**. As we had observed in related studies with the silyl amine **1** (see above),[1,2] photoreaction of these substrates in the aprotic solvent MeCN forms the silicon-containing adducts **20** exclusively. As with the systems investigated earlier, proton transfer in the contact ion pair **21** must be more rapid than desilylation when the basicity of the enone anion radical is not diminished by H-bonding interactions. In addition, the regioselectivity for this proton transfer process (i.e.,

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(9) Pienta, N. J. *J. Am. Chem. Soc.* **1984**, *106*, 2704. Pienta, N. J.; McKimmey, J. E. *Ibid.* **1982**, *104*, 5501. Smith, D. W.; Pienta, N. J. *Tetrahedron Lett.* **1984**, 915. Dunn, D. A.; Schuster, D. I.; Bonneau, R. *J. Am. Chem. Soc.* **1985**, *107*, 2802. Schuster, D. I.; Bonneau, R.; Dunn, D. A.; Dubien, J. J. *Ibid.* **1984**, *106*, 2706. Cookson, R. C.; Hudec, J.; Mirza, N. A. *J. Chem. Soc., Chem. Commun.* **1968**, 180.

(10) The $pK_a(H_2O)$ values for protonated enone anion radicals are ca. 10 (ref 10b) and the $pK_a(H_2O)$ values for amine cation radicals are ca. 8 (ref 10c). Thus, a strong thermodynamic driving force between amine cation and enone anion radicals, a requirement for rapid proton transfer when C–H bond cleavage is involved, does not exist in polar–protic solvents. However, in nonprotic media, proton transfer could be rapid (ref 10d), owing to an enhanced pK_a difference and the fact that charge anhilation is occurring. (b) Hayon, E.; Ibata, J.; Lichtin, N. N.; Simic, M. *J. Phys. Chem.* **1922**, *76*, 2072. Lilie, J.; Henglein, A. *Ber. Bunsengs. Phys. Chem.* **1969**, *73*, 170. (c) Das, S.; van Sonntag, C. *Z. Naturforsch.* **1986**, *416*, 505. (d) Shaefer, L. G.; Peters, K. S. *J. Am. Chem. Soc.* **1980**, *102*, 7566. Devadoss, C.; Fessenden, R. W. *J. Phys. Chem.* **1990**, *94*, 4540.
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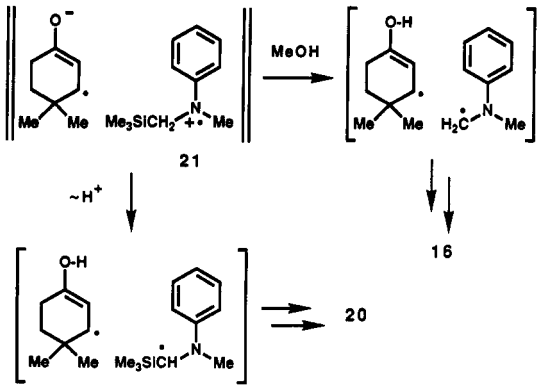

$TMSCH_2 > CH_3$) is fully consistent with a trimethylsilyl substituent effect on the kinetic acidity of cation radicals.[2,14]

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded by using a Bruker WP-200, AF-200 or AM-400 spectrometer and $CDCl_3$ solutions. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. For compounds containing Me_3Si groups, $CHCl_3$ was used as an internal standard. ^{13}C NMR resonances were assigned by use of the INEPT technique to determine numbers of attached hydrogens. IR spectra were recorded on a Perkin-Elmer 283 spectrometer. UV spectra were obtained on a Perkin-Elmer Lamda-5 spectrometer and mass spectra were recorded by using a Hewlett-Packard 580E (low resolution) or a VG-7700E (high resolution) mass spectrometer. Flash column chromatography was performed with Merck EM type 60 (230–400 mesh) silica gel. HPLC analyses were performed with a Perkin-Elmer Series 3B instrument and a C-18 reverse phase or Zorbax-sil normal phase column and 20% H_2O–MeOH or 10% EtOAc–hexane as respective eluants.

Preparative photochemical reactions were conducted with an apparatus consisting of a 450-W Hanovia medium pressure, mercury vapor lamp (ACE) surrounded by a uranium glass filter ($l > 320$ nm) in a water-cooled quartz immersion well surrounded by the solution being irradiated. The photolysis solutions were purged with argon both before and during irradiations. For photochemical reactions on which accurate product ratio analyses were performed, irradiations were conducted in sealed quartz tubes (100 mL), using an APQ 40 merry-go-round photoreactor. The reactor was equipped with a quartz well, uranium glass filter, and a 450-W medium pressure mercury lamp.

Irradiation of 4,4-Dimethylcyclohex-2-en-1-one (2) and *N,N*-Dimethylaniline (15). A solution of cyclohexenone **2** (112 mg, 0.90 mmol) and aniline **15** (108 mg, 0.90 mmol) in 90 mL of methanol was irradiated for 20 h (50% conversion of **2**). Concentration of the photolysate in vacuo gave a residue, which was subjected to molecular distillation to remove the remaining starting materials. The residue was subjected to column chromatography (10% ether–hexane), which afforded 16 mg (14%) of the non-TMS adduct **16**, 11 mg (10%) of the tricyclic adduct **17**, and a trace quantity of the tricyclic alcohol **18**.

A solution of the cyclohexenone **2** (116 mg, 0.90 mmol) and aniline **15** (108 mg, 0.90 mmol) in 90 mL of MeCN in a sealed quartz tube was irradiated for 20 h (35% conversion of **2**). Workup and purification as described above gave 6 mg (8%) of the non-TMS adduct **16** and a trace quantity of the tricyclic adduct **17**.

16: ^1H NMR 1.10 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.71–1.61 (m, 2 H, $CH_2C(Me)_2$), 2.45–2.05 (m, 5 H, $CH_2C(O)CH_2CH$), 2.89 (s, 3 H, *N*-Me), 2.99 (dd, J = 3.5, 10 Hz, 1 H, $CH(H)N$), 3.62 (dd, J = 3.1, 10 Hz, 1 H, $CH(H)N$), 6.64–6.70 (m, 3 H, Ar H), 7.15–7.23 (m, 2 H, Ar H); ^{13}C NMR 19.7 (CH_3), 28.6 (CH_3), 32.2 (C-4), 38.2 (C-5), 39.8 (C-3), 41.9 (C-6), 44.6 (C-2), 54.2 (C-7), 54.6 (CH_3N), 112.0 (ortho), 116.2 (para), 129.3 (meta), 149 (NAr), 211 (C=O); IR (neat) 2950, 2875, 1710, 1600, 1510, 1360, 750 cm^{-1}; mass spectrum, m/e (rel intensity) 245 (M^+, 2.3), 160 (1.2), 144 (1.4), 121 (8), 120 (100), 104 (6), 91 (3.3), 77 (12.9); high resolution mass spectrum, m/e 245.1783 ($C_{16}H_{23}NO$ requires 245.1780).

17: ^1H NMR 1.08 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.73 (M, 1 H, H-2e), 1.95 (ddd, J = 4.8, 6.8, 13.7 Hz, 1 H, H-3a), 2.29 (m, 1 H, H-4a), 2.36 (ddd, J = 4.8, 9.4, 14.2 Hz, 1 H, H-7e), 2.64 (ddd, J = 6.8, 13.7, 14.2 Hz, 1 H, H-2a), 2.87 (s, 3 H, CH_3N), 2.94 (dd, J = 5.5, 11.3 Hz, 1 H, H-5a), 3.21 (ddd, J = 2.0, 3.9, 11.3 Hz, 1 H, H-5e), 3.80 (d, J = 5.9 Hz, 1 H, H-10b), 6.60–6.69 (m, 2 H, Ar H), 6.82 (dd, J = 1.8 Hz, 1 H, Ar H), 7.10–7.20 (m, 1 H, Ar H); ^{13}C NMR 27.4 (Me), 32.1 (C-4), 35.9 (C-3), 37.8 (C-2), 37.9 (Me), 39.2 (C-4a), 46.1 (C-10b), 50.3 (C-5), 51.0 (C-N), 112.2 (C-7), 116.3 (C-9), 118.7 (C-10a), 128.5 (C-8), 140.0 (C-10), 145.8 (C-6a), 209.5 (C=O); IR (neat) 2960, 2875, 1715, 1605, 1510, 750 cm^{-1}; mass spectrum, m/e (rel intensity) 243 (M^+, 27.9), 214 (13.6), 186 (7.7), 160 (10.6), 144 (100), 91 (9.5), 77 (17.6); high resulution mass spectrum, m/e 243.1623 ($C_{16}H_{21}NO$ requires 243.1624).

18: ^1H NMR 0.91 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.73 (m, 2 H, H-3e,a), 1.81 (dd, J = 1.7, 4.6 Hz, 1 H, H-4a), 2.42 (ddd, J = 4.8, 7.3, 14.5 Hz, 1 H, H-2e), 2.70 (ddd, J = 14.5, 11.7, 6.0 Hz, 1 H, H-2a), 2.96 (s, 3 H, CH_3N), 3.26 (dd, J = 1.7, 12.5 Hz, 1 H, H-5e), 3.68 (dd, J = 4.6, 12.5 Hz, 1 H, H-5a), 4.50 (s, 1 H, OH), 6.49–6.66 (m, 3 H, Ar H), 7.11–7.21 (m, 1 H, Ar H); ^{13}C NMR 21.9 (Me), 30.9 (Me, 33.8 (C-4), 35.2 (C-3), 38.5 (C-4a), 41.1 (C-2), 47.6 (C-5), 51.7 (CH_3N), 77.6 (C—O), 110.8 (C-7), 115.9 (C-9), 120.3 (C-10a), 126.7 (C-8), 129.9 (C-10), 145.8 (C-6a), 213.6 (C=O); IR (neat) 3700–3100 (m), 2965, 2930, 2880, 1715, 1610, 1520, 750 cm^{-1}; mass spectrum, m/e (rel intensity) 259 (M^+, 36.5), 243 (5.1), 231 (26.0), 214 (11.7), 202 (8.8), 186 (8.1), 160 (100), 144 (16.6), 91 (6.2), 77 (9.0); high resolution mass spectrum, m/e 259.1574 ($C_{16}H_{21}NO$ requires 259.1572).

General Procedure for Determining the Effects of Reaction Conditions on Formation of Adducts 16 and 17 from Irradiation of 4,4-Dimethylcyclohex-2-en-1-one (2) and *N,N*-Dimethylaniline (15). Solutions of cyclohexenone **2** (1×10^{-2} M) and aniline **15** (1×10^{-2} M) in the specified solvent and containing the specified additives in 100-mL sealed quartz tubes were simultaneously irradiated in a merry-go-around apparatus. All samples were subjected to an argon purge for 15 min before being sealed and irradiated. The crude photolysates were concentrated in vacuo and then by molecular distillation. The ratios of adducts **16** and **17** were determined by HPLC (on a reversed phase column, see General section above) analysis and are given along with the respective solvent and additive in Table I.

Preparation of *N*-Methyl-*N*-[(trimethylsilyl)methyl]aniline (19). To a solution of 5.0 g (45 mmol) of *N*-methylaniline in 150 mL of THF under N_2 at −78 °C was added dropwise 40 mL of 0.129 M nBuLi (51 mmol). After the solution was stirred for 24 h and warmed to 25 °C, 11.0 g (51 mmol) of (iodomethyl)trimethylsilane was added slowly, and the resulting solution was stirred for 12 h at 25 °C, quenched by the addition of water, and concentrated in vacuo. The resulting aqueous solution was extracted with ether and the ethereal extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a residue, which was subjected to silica gel column chromatography (10% Et_2O–hexane) to yield 4.8 g (53%) of (silylmethyl)aniline **19**: ^1H NMR 0.08 (s, 9 H, $Si(CH_3)_3$), 2.84 (s, 2 H, CH_2Si), 2.91 (s, 3 H, NCH_3), 6.62–6.67 (m, 3 H, Ar H), 7.15–7.20 (m, 2 H, Ar H); ^{13}C NMR −1.2 ($Si(CH_3)_3$), 40.2 (NCH_3), 44.0 (NCH_2), 119.9 (ortho), 115.2 (para), 128.8 (meta), 150.6 (NAr); IR 2952, 2894, 2807, 1599, 1540, 1365, 1248, 1194, 1157, 854, 745, 691; mass spectrum, m/e (rel intensity) 193 (M^+, 10.4), 178 (6.6), 121 (8.7), 120 (100), 104 (6.0), 77 (10.1), 73 (15.0); high resolution mass spectrum, m/e 193.1288 ($C_{11}H_{19}SiN$ requires 193.1287).

Irradiation of 4,4-Dimethylcyclohex-2-en-1-one (2) and *N*-Methyl-*N*-[(trimethylsilyl)methyl]aniline (19). A solution of cyclohexenone **2** (112 mg, 0.90 mmol) and (silylmethyl)aniline **19** (174 mg, 0.90 mmol) in 90 mL of methanol and 4.5 mL of ethanol was irradiated for 10 h (74% conversion of **2**). Concentration in vacuo followed by molecular distillation to remove unreacted starting materials gave a residue, which was subjected to silica gel column chromatography (10% Et_2O–hexane) to give 104 mg (64%) of the non-TMS adduct **16** and a trace quantity (<1%) of the tricyclic adduct **17**.

A solution of cyclohexenone **2** (112 mg, 0.90 mmol) and (silylmethyl)aniline **19** (174 mg, 0.90 mmol) in 90 mL of acetonitrile

(14) In recent studies (Xu, W.; Mariano, P. S. *J. Am. Chem. Soc.*, in press), additional evidence verifying the acidifying effects of the TMS group in amine cation radical systems has been accumulated.

was irradiated for 10 h (70% conversion of **2**). Workup and chromatographic separation as described above gave 60 mg (29%) of the TMS adduct **20** (as a 1:1 mixture of diastereomers).

20: ^{1}H NMR 0.07 (s, 9 H, $Si(CH_3)_3$), 0.10 (s, 9 H, $Si(CH_3)_3$), 0.88 (s, 6 H, 2 CH_3), 1.04 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.51-1.63 (m, 5 H), 1.82 (dd, J = 5.8, 10.8 Hz, 1 H), 2.12-2.55 (m, 6 H), 2.58 (m, 2 H), 2.76 (s, 3 H, NCH_3), 2.94 (s, 3 H, NCH_3), 3.51 (d, J = 8.6, 1 H, CHN), 3.87 (s, 1 H, CHN), 6.55-6.73 (m, 6 H, Ar H), 7.11-7.25 (m, 4 H, Ar H); ^{13}C NMR -0.6 (Si-C), 0.6 (C-Si), 19.6, 20.3, 29.4, 29.5, 34.1, 37.7, 37.9, 40.8, 41.0, 42.0, 43.1, 43.4, 46.7, 49.6, 50.1, 111.2, 113.0, 114.9, 115.8, 129.0, 129.2, 148.9, 151.2, 210.9, 211.4; IR (neat) 2960, 2860, 1713, 1598, 1505, 1250, 860, 840, 750 cm^{-1}; mass spectrum, m/e (rel intensity) 317 (M^+, 1.4), 245 (5.6), 244 (31.6), 192 (19.7), 120 (13.4), 86 (66), 84 (100), 77 (7), high resolution mass spectrum, m/e 317.2176 ($C_{19}H_{31}SiNO$ requires 317.2175).

General Procedure for Determining the Effects of Reaction Conditions on Formation of Adducts 16 and 17 from Irradiation of 4,4-Dimethylcyclohex-2-en-1-one (2) and *N*-Methyl-*N*-[(trimethylsilyl)methyl]aniline (19). Solutions of cyclohexenone **2** (1×10^{-2} M) and aniline **19** (1×10^{-2} M) in the specified solvent and containing the specified additives in 100-mL sealed quartz tubes were simultaneously irradiated in a merry-go-around apparatus. All samples were subjected to an argon purge for 15 min before being sealed and irradiated. The crude photolysates were concentrated in vacuo and then by molecular distillation. The ratios of adducts **16** and **17** were determined by HPLC (on a normal phase column) analysis and are given along with the respective solvent and additive in Table I.

9,10-Dicyanoanthracene SET-Sensitized Photoreaction of 4,4-Dimethylcyclohex-2-en-1-one (2) and (Silylmethyl)aniline 19. Solutions of the cyclohexenone **2** and (silylmethyl)aniline **19** (0.2 M) in 4 mL of 20% MeCN-MeOH containing 9,10-dicyanoanthracene (6×10^{-6} M) were irradiated in a merry-go-round apparatus. The concentrations of **2** used in these simultaneous reactions were varied (0.2, 0.1, and 0.01 M). The photolysates were filtered and concentrated in vacuo and by molecular distillation to yield residues, which were analyzed for adduct **16** and tricyclic adduct **17** by HPLC on a reverse phase column.

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Supplementary Material Available: ^{13}C NMR spectra of **16**, **17**, **18**, **19**, and **20** (5 pages). Ordering information is given on any current masthead page.

Synthesis and Absolute Configuration of LY255582, a Potent Opioid Antagonist

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LY255582 ((+)-**1**) is a potent opioid antagonist recently discovered in our laboratories.[1] As a member of the phenylpiperidine class of opioid antagonists, the compound is structurally distinct from opioid antagonists currently used in clinical practice such as naloxone or naltrexone.[2] While the clinical importance of opioid antagonists in the treatment of narcotic overdose and drug-dependence is well established, recently other possible therapeutic applications for opioid antagonists have emerged, including the treatment of obesity, eating disorders, shock, spinal cord trauma, sexual dysfunction, and psychiatric conditions.[3,4]

Our synthetic strategy for the preparation of LY255582 is based on the coupling of the phenylpiperidine unit (+)-**2** with the cyclohexylpropanol fragment (-)-**3**. Preparation of each component in pure form ensured that the resulting coupled product would be of high enantiomeric purity. The coupling process itself provided a check on the resulting optical purity of the product, as formation of a diastereomeric mixture would result if either or both of the starting components suffered from enantiomeric contamination.

Assembly of the 3,4-dimethylphenylpiperidine nucleus with a high degree of optical purity was accomplished as shown in Scheme I. The aryltetrahydropyridine **4** was metalated with *n*-BuLi in THF at -20 °C, giving a deep red solution of the allylic anion, which was then alkylated with methyl iodide to give enamine **5** in 75% yield.[5,6] Introduction of the methyl group at the 3-position was accomplished with a two-step alkylation-reduction process adopted from Barnett.[7] The initial carbon-carbon bond formation was achieved by the Mannich reaction of enamine **5** with formaldehyde and dimethylamine to give an 86% yield of amino enamine **6**.

Establishment of the correct relative stereochemistry of the 3 and 4 stereocenters was then accomplished through reductive cleavage of the Mannich adduct **6**. Hydrogenolysis with 5% Pt/C afforded (±)-**8** by a stepwise process wherein the allylic amine is first cleaved, followed by reduction of the resulting methyl enamine. The choice of catalyst was crucial for optimizing stereoselectivity in the reduction process. The best degree of selectivity in the hydrogenolytic formation of (±)-**8** and its isomer (**14**—having the 3 and 4 methyl groups in a cis relationship) was obtained with the use of 5% Pt/C in EtOH, affording an 8:1 ratio favoring (±)-**8**. Unfortunately, this ratio of isomers became more nearly 1:1 on larger scale operations of the reaction. However, stereoselectivity could be preserved on scale-up if the reduction was broken up stepwise into its component parts of hydrogenolysis of the carbon-nitrogen bond followed by double-bond hydrogenation. This was readily accomplished due to the substantially slower rate of the second step of the operation. This rate differential could be enhanced through the use of deactivated catalysts such as $Pd/BaSO_4$. The resulting enamine double bond was then reduced with $NaBH_3CN$ in methanol to give a 13:1 ratio of isomers, the desired (±)-**8** predominating. Resolution of (±)-**8** into its optical antipodes was accomplished with dibenzoyl D- and L-tartrates. Evaluation of the enantiomeric purity of (+)-**9** and its antipode was performed by the use of the chiral NMR complexing reagent (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)-

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