Table I. UV Spectra of Cyclohexadienyl Cations

cation	solvent	λ_1(max)	ϵ_1, M^{-1}, cm^{-1}	λ_2(max)	ϵ_2, M^{-1}, cm^{-1}	$OD(\lambda_1)/OD(\lambda_2)$
$MESH^+$	HFIP[a]	355		260		1.27[b]
	HF/BF_3[c]	355	11000	254	8700	1.26
	$HCl/AlCl_3$/ImCl[d]	360	10700	262	10200	1.05
	CF_3SO_3H[e]	358				
$HMBH^+$	HFIP[a]	390		275		1.51[b]
	$HCl/AlCl_3$/ImCl[d]	396	9880	285	6700	1.47
	98% H_2SO_4[f]	395	≈10000	283	7240	1.38
$TMBH^+$	HFIP[a]	345		250		0.58[b]
	65% $HClO_4$[g]	346	10000	251	15000	0.65

[a] This work. [b] See footnote 9. [c] Dallinga, G.; Mackor, E. L.; Verrijn Stuart, A. A. *Mol. Phys.* **1958**, *1*, 123. [d] Smith, G. P.; Dworkin, A. S.; Pagni, R. M.; Zingg, S. P. *J. Am. Chem. Soc.* **1989**, *111*, 525. ImCl is 1-ethyl-3-methylimidazolium chloride. [e] Bokoss, H. J.; Ransom, R. J.; Roberts, R. M. G.; Sadri, A. R. *Tetrahedron* **1982**, *38*, 623. [f] Deno, N. C.; Groves, P. J.; Jaruzelski, J. J.; Lugasch, M. N.; *J. Am. Chem. Soc.* **1960**, *82*, 4719. [g] Kresge, A. J.; Chiang, Y.; Kakke, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 6167.

Table II. Quantum Yields for Formation of Cyclohexadienyl Cations and Rate Constants for Decay at 20 ± 1 °C

cation	solvent	Φ[a]	k(decay), s^{-1}
$MESH^+$	HFIP	0.08	1×10^5
$HMBH^+$	HFIP	0.04	7×10^3
$TMBH^+$	HFIP	0.06	$<1 \times 10^2$
$TMBH^+$	TFE	~0.006	7×10^2
$TMBH^+$	1:4 AN:H_2O	~0.003	5.8×10^5
$TMBH^+$	0.4 M $HClO_4$ (20% AN)	0.01	3.2×10^5
$TMBH^+$	3 M $HClO_4$ (20% AN)	0.03	6.3×10^4

[a] See footnote 9.

Table III. Rate Constants, k_{Nu} for the Reaction of Bases/Nucleophiles Nu with $MESH^+$, $HMBH^+$, and $TMBH^+$ in HFIP at 20 ± 1 °C

Nu	k_{Nu},[a] M^{-1} s^{-1}		
	$MESH^+$[b]	$HMBH^+$[c]	$TMBH^+$[d]
H_2O	8.8×10^6	2.7×10^5	<10
MeOH	2.4×10^7	1.5×10^6	$<10^2$
EtOH	1.7×10^7	8.2×10^5	$<10^2$
i-PrOH	2.0×10^7	8.1×10^5	$<10^2$
t-BuOH	1.2×10^7	8.7×10^5	$<10^2$
tetrahydrofuran	2.0×10^7	2.1×10^6	34
1,4-dioxane	5.4×10^6	1.3×10^5	
$C_2H_5OCH{=}CH_2$	$\approx 2.2 \times 10^6$	$\approx 1.6 \times 10^5$	
$CH_2(CH_2)_2CH{=}CHO$	5.6×10^6	3.0×10^5	
$CH_2(CH_2)_3CH{=}C(Me)$	$\approx 9 \times 10^6$	$\approx 9 \times 10^5$	
Cl^-[e]	2.4×10^9	4.3×10^8[f]	$\leq 5 \times 10^2$[f]
Br^-[e]	3.7×10^9	6.3×10^8[f]	$\leq 10^3$[f]
I^-[e]	3.8×10^9	1.1×10^9[f]	
NO_3^-[e]	1.4×10^9	1.7×10^8[f]	

[a] Error limits typically ±10%. [b] Monitored at 355 nm. [c] Monitored at 390 nm. [d] Monitored at 345 nm. [e] Counterion is $(n\text{-Bu})_4N^+$. [f] Reaction is possibly reversible. If this is the case, the measured k_{Nu} is *not* identical with the rate constant for ion combination.

results, e.g., the second-order rate constants for the reaction of $MESH^+$ and $HMBH^+$ in HFIP with alcohols, ethers, and halides. With the series of alcohols there is obviously very little steric effect, even for *t*-BuOH. Since the basicities of these compounds are similar, it is this factor that determines reactivity. This also explains why tetrahydrofuran, which has similar basicity, reacts at a rate similar to the alcohols, while 1,4-dioxane, which is less basic due to the inductive ($-I$) effect of the additional oxygen, is less reactive. In comparison, the very high reactivity of the three halides and of NO_3^- suggests that these do not react as bases, but rather by nucleophilic combination with the cyclohexadienyl cations.[10] With all the bases/nucleophiles, $HMBH^+$ reacts considerably slower than does $MESH^+$, which is obviously due to the higher degree of stabilization and steric demand of $HMBH^+$. As seen from column 4 of Table III, $TMBH^+$ has an astounding lack of reactivity in HFIP toward bases/nucleophiles.

Detailed studies of the reactivities with additional reagents, as well as extensions to other aromatic systems, are currently in progress. The present study demonstrates that the solvent HFIP has the remarkable properties of a very weak basicity/nucleophilicity combined with good photoprotonating capabilities. Thus the photolysis of aromatic compounds in this solvent provides an excellent method for generating and observing unstable cyclohexadienyl cations. Moreover the reactivities of the so-formed cations with the solvent and with added bases/nucleophiles can be directly examined.

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(10) See note *f* in Table III.

Picosecond Flash Photolysis of Carboxy Horseradish Peroxidase: Rapid Geminate Recombination in the Presence of Benzohydroxamic Acid

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Photolysis of heme–CO bonds occurs on the femtosecond time scale.[1] Photolysis quantum yields (Φ) of less than 1, as measured on micro- or millisecond time scales, have been ascribed to fast geminate recombination of CO with the heme.[2] In sperm whale myoglobin (Mb), most of the CO molecules pass through the protein matrix into the solvent at room temperature[3] and Φ is very near unity,[4,5] but for ferrohorseradish peroxidase (HRP), a Φ of less than 1 has been reported.[5] A smaller Φ for HRP compared to Mb is consistent with the proposed lower barrier for CO binding to the heme in the peroxidase,[6] since this would allow rapid

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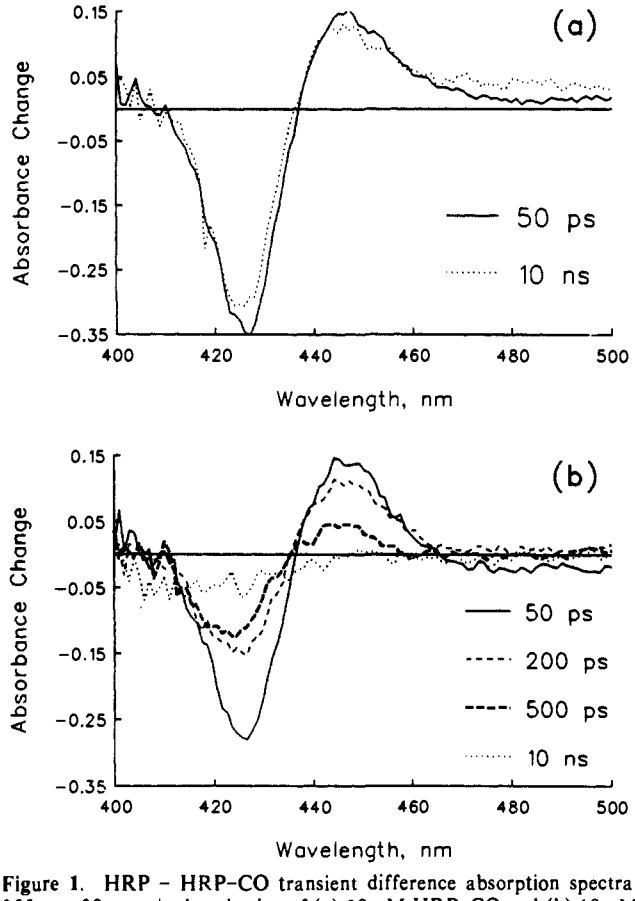

Figure 1. HRP - HRP-CO transient difference absorption spectra: 355-nm, 30-ps pulsed excitation of (a) 20 μM HRP-CO and (b) 18 μM HRP-CO + 10 mM BHA in 0.1 M phosphate buffer, pH 7, 22 ± 1 °C, yielded the spectra recorded at the delay times between the pump and probe beams indicated. Each trace is an average of six independent measurements, and the errors in the optical densities are ≤±0.015 at λ > 410 nm. The 10-ns spectrum in part a shows absorbance at λ > 460 nm which extends out to the end of the continuum at 600 nm. The origin of this base-line shift, which varies from sample to sample, is being investigated.

geminate recombination. Increasing the steric constraints on the geminate ligand in the heme pocket should also increase the fraction of geminate recombination by hindering CO escape to the solvent. Benzohydroxamic acid (BHA) is a reducing substrate for HRP and binds in the vicinity of its heme.[7] Vibrational spectroscopic studies reveal that in the ternary BHA-HRP-CO complex there is a single nonlinear Fe-C-O conformer in which the bound CO is tilted over the heme plane.[8] Since tilting of the CO suggests steric interactions between BHA and the bound ligand,[8] occupation of the BHA binding site should modify the heme-CO binding kinetics.

To probe the effects of BHA binding on CO recombination of HRP, solutions containing 0–10 mM BHA, 1 mM CO, and 5 μM HRP were photolyzed by using a 10-μs xenon flash.[9] Addition of BHA reduced the transient signal intensity, which leveled off at ≤20% of the free HRP value in the presence of ≥6 mM BHA.[10,11] To decrease the microsecond photolysis yield, BHA binding either reduces the efficiency of photochemical cleavage of the Fe^{2+}–CO bond in HRP or increases the fraction of geminate recombination. To distinguish between these possibilities, photolysis of the HRP-CO samples was carried out using 30-ps, 2.5-mJ, 355-nm pulses,[12] and the transient difference absorption spectra (HRP-HRP-CO) recorded between 50 ps and 10 ns are shown in Figure 1. Clearly, the 50-ps spectra are similar in the presence and absence of BHA; minima and maxima are observed at 424 and 445 nm due to bleaching of HRP-CO absorption and the growth of HRP absorption, respectively.[14] However, the 10-ns spectra of BHA-bound HRP shows ~90% recovery to the preflash base line, whereas in the absence of BHA an average of only ~20% recovery was observed for three different samples.

The picosecond data clearly indicate that rapid geminate CO recombination occurs extensively in BHA-bound HRP at room temperature, which accounts for the low microsecond photolysis yield observed for BHA-HRP relative to free HRP.[15] Kinetic analysis of the change in ΔA vs time[16] indicates that geminate recombination of BHA-HRP shows reasonable first-order behavior with a rate constant of 2×10^9 s^{-1} over 3 half-lives (~1 ns). Picosecond geminate recombination also occurs in free HRP at room temperature. However, extraction of meaningful kinetic information from the transient spectra obtained in the absence of BHA is not possible because the observed absorbance changes are small relative to the noise of the picosecond spectrometer (±0.015A). Therefore, we cannot tell with confidence from the picosecond experiments if BHA binding alters the kinetics, as well as the fraction of geminate recombination in HRP.

CO recombination to BHA-HRP is 250–400-fold faster than the rates estimated for CO geminate recombination to sperm whale Mb.[3,17] In fact, CO recombination to BHA-HRP is only ~10-fold slower than the picosecond phase of O_2 and isocyanide geminate recombination to Mb at room temperature, where the ligand supposedly remains within a few angstroms of the Fe atom.[2] Therefore, we propose that occupation of the BHA binding site in HRP traps ~90% of the photodissociated CO molecules close to the Fe atom. In the absence of BHA, many more of the CO molecules are free to wander the heme cavity, escape into solution, and recombine with the heme in ≥100 ms.[9]

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(9) HRP-CO was formed upon addition of ~25 μM dithionite to ~5 μM ferri-HRP (Boehringer Mannheim, grade I) in CO-saturated, 0.1 M phosphate buffer, pH 7, in a 1-cm Pyrex cell. Successive additions of BHA (Aldrich, 99% pure) were made from a deaerated stock solution by using a gas-tight syringe to give a range of BHA concentrations between 0 and 10 mM. At ~100 ms after photolysis, decay of the transient absorption of HRP and of the transient bleaching of HRP-CO indicated the onset of slow bimolecular CO recombination ($t_{1/2}$ ~ 0.2 s) as previously reported (Coletta, M.; Ascoli, F.; Brunori, M.; Traylor, T. G. *J. Biol. Chem.* **1986**, *261*, 9811).

(10) Saturation of the BHA binding site is expected in this concentration range since the dissociation constant of the BHA complex of ferro-HRP is $(3 \pm 2) \times 10^{-4}$ M.[11]

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(12) Solutions of ~20 μM HRP-CO in 0.1 M phosphate buffer, pH 7, were prepared in the presence and absence of 10 mM BHA by adding 1 mM dithionite to CO-saturated ferri-HRP solutions in 2-mm cuvettes. The picosecond laser system at Concordia is similar to that described previously,[13] and photolysis of a solution of horse heart Mb-CO yielded Mb - Mb-CO picosecond difference spectra that are essentially identical with those reported for sperm whale Mb.[13] Also, the optical densities in our Mb transient spectra indicate that the intensity of the pump beam is sufficient to completely photolyze the samples.

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(14) The wavelengths of the absorption minimum and maximum in the HRP - HRP-CO static difference spectrum recorded on a diode-array spectrophotometer (HP Model 8451A) are 422 and 442 nm, respectively, indicating a 2–3-nm red shift in the picosecond transient difference spectra. Since the Mb - Mb-CO picosecond transient difference spectra show similar red shifts unless a PMT is used,[13] the shifts observed here for HRP are attributed to the response of the Vidicon.

(15) Using horse heart Mb-CO as a standard (Φ = 1.0),[5] microsecond Φ's of 0.65 and 0.13 were obtained for free HRP-CO and BHA-HRP-CO, respectively (Hill, B. C.; Marmor, S., unpublished results). A Φ of 0.70 has been published for free HRP.[5]

(16) Transient spectra were obtained for BHA-HRP at eight different delay times between 50 ps and 1 ns. First-order kinetic analysis of the change in ΔA ($=\Delta A_{445} - \Delta A_{424}$) vs time was carried out by plotting ln $(\Delta A_t - \Delta A_\infty)$ vs t, where $\Delta A_\infty = \Phi \Delta A_0$, Φ = 0.13,[15] and ΔA_0 was calculated from the known extinction coefficients of HRP and HRP-CO[11] assuming complete photolysis.[12] The fit of the data points, including ΔA_0, to a straight line gave a correlation coefficient of 0.99. The ΔA at 10 ns was not included in the analysis because of the low signal-to-noise ratio in this spectrum (Figure 1b).

(17) Below 180 K, binding of CO to sperm whale Mb reportedly occurs mainly from the heme cavity, and extrapolation of the low-temperature rates to room temperature yielded a geminate rate constant of 8×10^6 s^{-1} (Ansari, A.; DiIorio, E. E.; Dlott, D. D.; Frauenfelder, H.; Iben, I. E. T.; Langer, I. P.; Roder, H.; Sauke, T. B.; Shyamsunder, E. *Biochemistry* **1986**, *25*, 3139).

Since HRP binds a large number of aromatic substrates,[11,18] it should be possible to gain insight into which substrates can alter its heme–CO recombination kinetics at room temperature. Thus, picosecond studies using different aromatic donors are planned, and these investigations should yield information complementary to any future results on mutant peroxidases.

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((9-Fluorenylmethyl)oxy)carbonyl (FMOC) Amino Acid Fluorides. Convenient New Peptide Coupling Reagents Applicable to the FMOC/*tert*-Butyl Strategy for Solution and Solid-Phase Syntheses

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Recently FMOC amino acid chlorides were found to be stable highly reactive reagents for peptide-bond formation[1] which, in view of their favorable properties, were adopted as key intermediates in a new technique for the rapid, continuous synthesis of short peptide segments.[2] Applications to solid-phase syntheses have also been described.[3] Unfortunately, the impossibility of obtaining stable FMOC amino acid chlorides from trifunctional amino acids bearing side-chain protection incorporating the *tert*-butyl moiety (*t*-BOC, *tert*-butyl esters, *tert*-butyl ethers, etc.) seriously limits the applicability of this class of coupling agents. For example, attempts to obtain FMOC-aspartic acid chloride β-*tert*-butyl ester from **1** (n = 1) gave only the cyclic anhydride **3** by loss of *tert*-butyl chloride from the presumed intermediate acid chloride **2**. The same reaction occurred even in the case of the less sensitive β-1-adamantyl ester[4] related to **1**. Similarly stable, crystalline FMOC amino acid chlorides are not obtainable from glutamic acid γ-*tert*-butyl ester **1** (n = 2), ϵ-BOC-lysine, and the *O*-*tert*-butyl ethers of serine, threonine, and tyrosine.

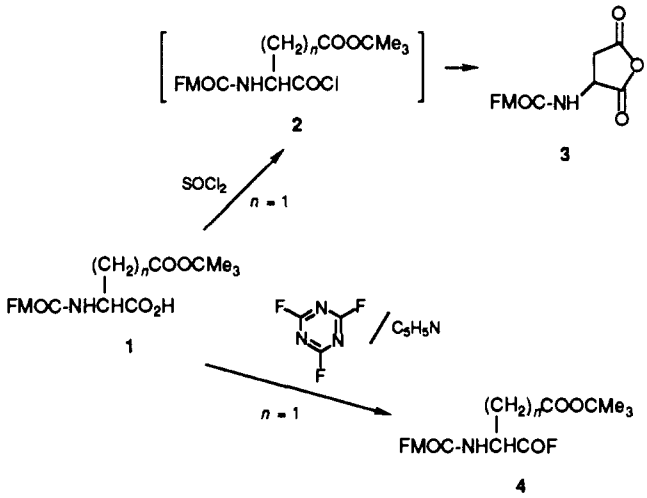

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Table I. FMOC Amino Acid Fluorides[a,b]

compound	yield (%)	mp (°C)	optical rotation, $[\alpha]_D$, t (°C)
FMOC-Gly-F	80.5	140–141	
FMOC-Ala-F	75.4	111–112	+3.6° (*c* 0.5, EtOAc), 23
FMOC-Val-F	70.2	113–114	+10.7° (*c* 1, CH_2Cl_2), 24
FMOC-Leu-F	75.2	95–96	−7.9° (*c* 1, EtOAc), 23
FMOC-D-Leu-F	75.0	96–97	+7.6° (*c* 1, EtOAc), 23
FMOC-Ile-F	73.3	115–116	+15.6° (*c* 0.5, EtOAc), 23
FMOC-Pro-F	78.2	88–89	−28.6° (*c* 0.5, EtOAc), 24
FMOC-Phe-F	63.9	118–120	+35.5° (*c* 1, CH_2Cl_2), 24
FMOC-Trp-F[c]	70.7	125–128	−5.2° (*c* 1, EtOAc), 24
FMOC-Ser(*t*-Bu)-F[c]	72.7	89–91	+28.8° (*c* 0.5, EtOAc), 26
FMOC-Thr(*t*-Bu)-F[c]	72.6	53–55	+12.3° (*c* 0.4, EtOAc), 27
FMOC-Lys(BOC)-F[c]	80.0	128–130	−2.2° (*c* 0.5, CH_2Cl_2), 24
FMOC-Asp(O-*t*-Bu)-F[c]	67.8	74–75	+4.0° (*c* 0.5, EtOAc), 23
FMOC-Met-F	72.0	137–139	−12.9° (*c* 0.55, EtOAc), 25
FMOC-Glu(O-*t*-Bu)-F[c]	71.5	80–82	−11.2° (*c* 0.5, EtOAc), 25
FMOC-Tyr(*t*-Bu)-F[c]	67.4	97–99	+33.0° (*c* 0.5, CH_2Cl_2), 25
FMOC-Phg-F	75.0	144–146	+97.5° (*c* 0.5, CH_2Cl_2), 25

[a] All reactions involving the synthesis of cyanuric fluoride and the derived FMOC amino acid fluorides were carried out in ordinary glass vessels without any evidence of etching, etc. For a representative example of conversion to the acid fluoride, a solution of 0.339 g (1 mmol) of FMOC-Val-OH in 5 mL of CH_2Cl_2 was refluxed under N_2 with 1.08 g (8 mmol,[d] 700 μL, d = 1.6) of cyanuric fluoride and 81 μL (1 mmol) of pyridine for 2 h. The mixture, from which a water-soluble white precipitate had settled, was extracted with two 15-mL portions of ice water. Removal of solvent from the dry ($MgSO_4$) organic layer gave a white solid, which was recrystallized from CH_2Cl_2/hexane to give the pure acid fluoride. Detection of residual acid by TLC or analysis of fluoride content by HPLC was carried out as described earlier[1] after addition to dry MeOH except that it was necessary to wait for 15–300 min to allow time for complete conversion to methyl ester. For example, a solution analyzing initially for 82.7% FMOC-Val-F (as Me ester) came to complete conversion after 5 h with a measured content of 98.2% FMOC-Val-OMe and 0.9% FMOC-Val-OH. Esterification of the residual FMOC amino acid in the resulting methanolic HF solution did not occur, in contrast to the analogous acid chloride case. [b] In all cases, elemental analyses for C, H, and N agreed with theoretical values (±0.3%). [c] In these cases, the reaction mixtures were stirred at room temperature for 0.5–1.5 h. [d] More recently it was found convenient to use only 2 mmol of cyanuric fluoride with stirring at room temperature for 3 h for all fluorides listed in the table.

The long-known marked stability of *tert*-butyl fluoroformate relative to that of the corresponding chloro analogue[5,6] prompted an examination of FMOC amino acid fluorides. Our expectations were fully realized, and the remarkable reagents obtained have proved to be an exceptionally useful category of peptide coupling agents.

With the readily available reagent cyanuric fluoride,[7] aspartic acid ester **1** (n = 1) gave the stable, crystalline acid fluoride **4** (n = 1). Similarly other acid-sensitive protected amino acids (e.g., ϵ-BOC-FMOC-lysine, FMOC-glutamic acid γ-*tert*-butyl ester, the *O*-*tert*-butyl ethers of serine, threonine, and tyrosine, and unprotected tryptophan) were converted to the corresponding FMOC amino acid fluorides without difficulty. Table I collects the fluorides so far synthesized along with key physical properties.[8]

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(8) The infrared and especially the ^{13}C NMR data for model compounds FMOC-Val-Cl and FMOC-Val-F provide clear evidence for the simple acid halide structure of these compounds: (a) IR (KBr) 1790 (ClC=O), 1843 cm^{-1} (FC=O); (b) ^{13}C NMR ($CDCl_3$) 174.6 (ClC=O), 161.9 ppm (d, J_{CF} = 285.5 Hz, FC=O). For the acid fluoride, the expected carbon–fluorine coupling was also observed for the α-carbon atom: 58.2 ppm (d, J_{CF} = 38.5 Hz). The ^{13}C NMR position of the carbonyl group in the oxazolone[9] [mp 82–84 °C or 90–92 °C, α^{23}_D −29.6° (*c* 0.5, CH_2Cl_2)] derived from FMOC-Val-OH (obtained in an analytically pure state) is 175.3 ppm.[10] H–F coupling is also observed for the α-CH unit in the ^1H NMR spectrum (DMF-d_7) of FMOC-Phg-F (δ 5.7, dd).

(9) Compare: Paquet, A.; Chen, F. M. F.; Benoiton, N. L. *Can. J. Chem.* **1984**, *62*, 1335. Paquet et al. obtained a crude sample of this compound contaminated with 15% of dibenzofulvene.

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