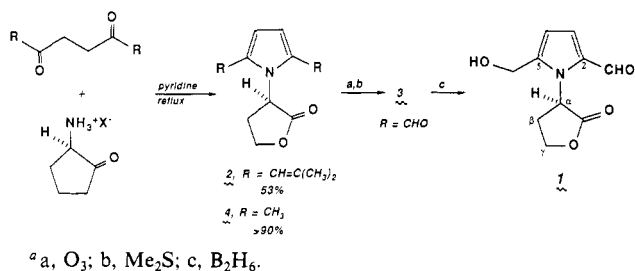


Scheme I Synthesis of **1**^a

by IR and restricted the neutral fragment of C₄H₅O₂ to a γ -lactone bound to the pyrrole nitrogen. Two ¹H NMR resonances,^{9a} which appeared on cooling and resolved as a doublet (δ 5.70, α -) and a pentet (δ 2.67, β -H) at -20 °C, were anisotropically broadened by hindered rotation of the N-C bond.^{9b} Conversion to the symmetrical dialdehyde **3** (400 μ g, MnO₂, CH₃CN, 1 h, \sim 100%)¹⁰ gave sharp ¹H NMR resonances at ambient temperature,¹¹ further supporting **1**.

Paal-Knorr condensation¹² of acetonyl acetone with α -aminobutyrolactone-HBr (pyridine, reflux, 4 h, 89%) afforded the dimethylpyrrole **4**. Oxidation of **4** with benzeneseleninic anhydride¹³ (1.3 equiv, PhCl, 18 h, reflux, 34%) gave the monoaldehyde **5** which could not be further oxidized. However, condensation of the aminolactone with 2,9-dimethyldeca-2,8-dien-4,7-dione¹⁴ gave the bis(isobutenyl)pyrrole **2** (53%), which on ozonolysis (O₃, CH₂Cl₂, Me₂S workup) followed by diborane reduction (THF, 0 °C) gave **1** in good yields (Scheme I). Condensation of the chiral α -aminobutyrolactone¹⁵ gave **2** (\sim 20% racemization, resolved by repeated recrystallization from ether/petroleum ether (R , [α]_D²³ -288 (c 0.0036, CHCl₃)) afforded both (+)- and (-)-**1**. Mosher's acid esterification¹⁷ (1.2 equiv, R -(+), pyridine, 0 °C, 12 h) allowed for HPLC analysis (Zorbax ODS, 48% MeCN/H₂O 2 mL/min; R_1 (R,R) = 7.8 min, (S,R) = 7.3 min) of the resulting diastereomers. Similar derivatization of the natural product confirmed its R absolute configuration.

The ED₅₀⁵ of exogenously added **1** (S isomer shows no activity) in the inhibition of trigonelline-induced cellular arrest in G2 is

(9) (a) ¹H NMR (500 MHz, C₂D₆O, -20 °C) δ 9.48 (1 H, s, CHO), 7.20 (1 H, d, J = 4 Hz, H-3), 6.37 (1 H, d, J = 4 Hz, H-4), 5.70 (1 H, dd, J = 12, 10 Hz, α -H), 4.80 (2 H, AB, J = 15 Hz, CH₂OH), 4.67 (1 H, dt, J = 10, 1.6 Hz, γ -H), 4.53 (1 H, ddd, J = 11, 10, 9.5 Hz, γ -H), 2.82 (1 H, bq, J = 10, 1.6 Hz, β -H), 2.67 (1 H, p, J = 11 Hz, β -H). (b) The coalescence temperature for **1** is 40 °C with an approximate ΔG^\ddagger of 14.7 cal/m. Oki, M. *Methods in Stereochemical analysis*; Marchand, A. P., Ed.; VCH Publishers: 1985; Chapter 5 and references therein.

(10) Goldman, I. M. *J. Org. Chem.* **1969**, *34*, 1979-1981.

(11) ¹H NMR (500 MHz, CDCl₃) δ 9.80 (2 H, s, CHO), 7.10 (2 H, s, H-3, 4), 6.66 (1 H, dd, J = 10.5, 9 Hz, α -H), 4.74 (1 H, dt, J = 10, 2.5 Hz, γ -H), 4.50 (1 H, m, γ -H), 2.76 (1 H, m, β -H), 2.69 (1 H, m, β -H).

(12) Young, D. M.; Allen, C. F. H. *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. 2, p 219-220. Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*; W. A. Benjamin: New York, 1968; pp 102-149.

(13) Barton, D. H. R.; Hui, R. A. H. F. Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2179-2185.

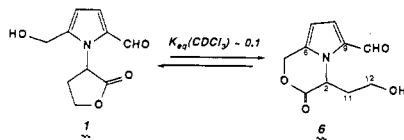
(14) Obtained from Cu-promoted dimerization of mesityl oxide enolate. Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912-2914.

(15) Obtained from lactonization of L-homoserine¹⁶ (6 N HCl, 6 h; L, (α)_D²³ 27.0 (c 0.05 H₂O)) or from acylase 1 hydrolysis of the N -chloroacetate of racemic homoserine lactone D, (α)_D²³ +26.0 (c 0.05, H₂O). Birnbaum, S. M.; Greenstein, J. P. *Arch. Biochem. Biophys.* **1953**, *42*, 212-48.

(16) Armstrong, M. D. *J. Am. Chem. Soc.* **1949**, *71*, 3399-3402.

(17) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

(18) During isolation, **1** was found to be sensitive to racemization and in CDCl₃ to intramolecularly transacylate to the fused ring system **6**: ¹H NMR (500 MHz, CDCl₃) δ 9.49 (1 H, s, CHO), 7.04 (1 H, d, J = 3 Hz, H-8), 6.25 (1 H, d, J = 3 Hz, H-7), 5.62 (1 H, d, J = 14.7 Hz, H-5), 5.37 (1 H, d, J = 14.7 Hz, H-5'), 5.84 (1 H, t, J = 6.3 Hz, H-2), 3.73 (1 H, m, J = 12.8, 6 Hz, H-12), 3.44 (1 H, m, J = 12, 8, 4 Hz, H-12), 2.40 (2 H, m, H-11).



5×10^{-7} M. By harvesting tissues from roots of various ages, we have found that this concentration is reached within the tissue only in roots greater than 7 days of age. Thus, the presence of **1** could completely account for the inability of trigonelline to induce G2 arrest in older roots.⁵ The biological reason for this antagonism is not known, but **1** becomes the first chemically characterized substance which overrides hormonally induced cellular arrest in complex tissues.

MS/MS experiments on the hybrid BEQQ spectrometer very efficiently established the functional groups and their structural arrangement as seen in **1**. The substitution pattern of the pyrrole does not suggest obvious biosynthetic pathways; however, one possibility would involve a reductive amination of amino and keto acid precursors similar to the opines.¹⁹ This class of eucaryotic non-protein amino acids are biosynthesized in higher plants only when plasmid genes (T-DNA) of *A. tumefaciens* coding for the appropriate dehydrogenase are transferred and genetically incorporated into the plant genome. The characteristic (R) configuration in the products of these dehydrogenases is seen in **1** and preliminary experiments suggest that opines either serve as precursors or activate the synthesis of **1**. The significance of such a pathway and its role in cell cycle control are under investigation.

Acknowledgment. We are grateful to Jeffrey Shabanowitz for the initial MS/MS studies, S. Neighbors and S. Walker for preliminary isolation work, and The University of Chicago Cancer Center and Ciba-Geigy Corporation for support. D.G.L. is a Sloan Foundation Fellow and a Camille and Henry Dreyfus Teacher-Scholar.

(19) Tempe, J.; Goldmann, A. *Molecular Biology of Plant Tumors*; Schell, J., Nester, E. W., Eds.; Academic Press: New York, 1982; pp 427-49.

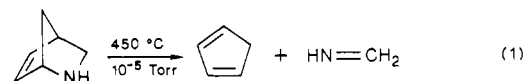
Retro Aza Diels-Alder Reactions: Acid-Catalyzed Heterocycloreversion of 2-Azanorbornenes in Water at Ambient Temperature

Paul A. Grieco,* David T. Parker, William F. Fobare, and Robert Ruckle

Department of Chemistry, Indiana University
Bloomington, Indiana 47405

Received April 27, 1987

The retro Diels-Alder reaction has received considerable attention during the past 20 years with emphasis on synthetic and mechanistic aspects.¹ In sharp contrast the imino variant of the retro Diels-Alder reaction² has received very little attention which is undoubtedly due in part to the fact that such retro Diels-Alder reactions have commonly been conducted at temperatures in the range of 400-600 °C (cf. eq 1).^{2a} These observations are not



surprising since it is well known that norbornene is resistant to thermolysis, requiring temperatures in excess of 250 °C.³ In striking contrast to the chemistry outlined in eq 1 we now report that 2-azanorbornene as well as its N -alkyl derivatives undergoes acid-catalyzed retro Diels-Alder reaction at room temperature in water.

(1) Ripoll, J.-L.; Rouessae, A.; Rouessae, F. *Tetrahedron* **1978**, *34*, 19. Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121.

(2) (a) Braillon, B.; Lasne, M.-C.; Ripoll, J.-L. *Nouv. J. Chim.* **1982**, *6*, 121. (b) Srinivasan, R.; Studebaker, J.; Brown, K. H. *Tetrahedron Lett.* **1979**, 1955. (c) Lasne, M.-C.; Ripoll, J.-L.; Thuillier, A. *J. Chem. Res.* **1982**, 214.

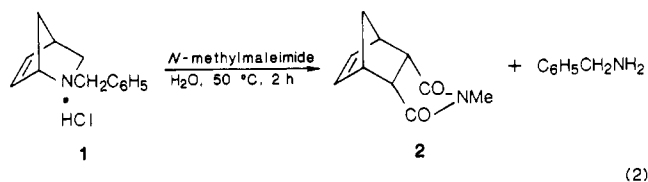
(3) Walsh, R.; Wells, J. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 52.

Table I. Acid-Catalyzed Retro Aza Diels–Alder Reaction of 2-Azanorbornene and Its *N*-Alkyl Derivatives^a

entry	azanorbornene	temp, °C	time, h	% yield of 2 ^b	% yield of primary amine ^b
1 ^c		50	5	80	
2 ^d		50	2	91	81
3 ^d		50	2	69	
4 ^d		50	4	73	85
5 ^e		50	5	89	
6 ^e		50	4	94	61 ^f
7 ^e		23	4		95
8 ^e		23	4		97

^aAll reactions were carried out in water containing 1.3 equiv of *N*-methylmaleimide employing the corresponding amine hydrochloride salts with the exception of entry 1 where acetic acid was employed. The concentration of amine hydrochloride in water ranged from 1.0–2.0 M. ^bIsolated yields. ^cPrepared as the acetic acid salt in 99% yield by reaction of phenacylamine hydrochloride with formaldehyde and cyclopentadiene in water followed by reductive cleavage employing zinc in acetic acid. ^dPrepared as detailed in ref 4. ^ePrepared according to the general procedure (ref 4) in >90% yield. ^fThe corresponding Pictet–Spengler cyclization product was isolated in 18% yield.

During our studies on the cyclocondensation of simple iminium salts with cyclopentadiene in water,⁴ we observed that *N*-benzyl-2-azanorbornene upon prolonged standing in air slowly leads to discoloration accompanied by evolution of cyclopentadiene. This heterocycloreversion process can be dramatically accelerated in water containing a trapping agent. When a 2.0 M solution of *N*-benzyl-2-azanorbornene hydrochloride (**1**) in water was heated at 50 °C for 2 h in the presence of *N*-methylmaleimide (eq 2),



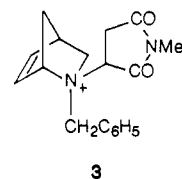
Diels–Alder adduct **2** (lit.⁵ mp 105–106 °C) and benzylamine were isolated in 91% and 81% yields, respectively. The reaction depicted in eq 2 can be carried out at ambient temperature; however, 20 h are required in order to realize a 60% yield of adduct **2**. The

(4) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

(5) Culberson, C. F.; Wilder, P., Jr. *J. Org. Chem.* **1960**, *25*, 1358.

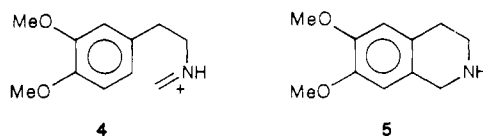
(6) 2-Azanorbornene hydrochloride⁴ readily undergoes heterocycloreversion at ambient temperature. For example a 1.0 M solution of 2-azanorbornene HCl in water containing excess *N*-methylmaleimide provided after 14 h a 60% yield of Diels–Alder adduct **2**. Reactions conducted at room temperature are heterogeneous and require vigorous stirring.

reaction can also be carried out on the free amine in the presence of *N*-methylmaleimide, in comparable yield; however, the reaction rate is appreciably slower. In the absence of *N*-methylmaleimide the free amine does not undergo retro Diels–Alder reaction. The above results suggest that heterocycloreversion of 2-azanorbornenes is catalyzed by acid and that the reactive species is an ammonium salt. However in the absence of added acid the cycloreversion process appears to be catalyzed by *N*-methylmaleimide presumably through the formation of ammonium salts such as **3**.



Remarkably, the retro aza Diels–Alder reaction of *N*-benzyl-2-azanorbornene does not proceed in organic solvents at 50 °C. In separate experiments employing benzene, tetrahydrofuran, and acetonitrile at 50 °C no trace of retro adduct **2** could be detected. However traces of the *N*-methylmaleimide adduct **2** could be detected after 2.5 h when the reaction was conducted at elevated temperatures in tetrahydrofuran (sealed tube, 75 °C) and benzene (sealed tube, 85 °C). Interestingly use of acetonitrile (sealed tube, 85 °C) as solvent provided a 38% yield of **2** after 2.5 h. In general the retro aza Diels–Alder reaction of 2-azanorbornenes is best conducted on the hydrochloride salts in water at 50 °C in the presence of *N*-methylmaleimide. Under these conditions, reactions are homogeneous and dramatically accelerated.

The retro aza Diels–Alder reaction is applicable to a number of *N*-alkyl-2-azanorbornenes (Table I). As indicated in Table I all reactions were conducted at 50 °C over a 2–5-h period employing azanorbornenes as their hydrochloride salts. Yields vary from good to excellent. Notable among the entries in Table I is the parent amine, 2-azanorbornene, which undergoes the retro Diels–Alder reaction at 50 °C in water (entry 1) which stands in sharp contrast to the conditions outlined in eq 1. Also of interest is the heterocycloreversion depicted in entry 6 which gives rise to a 61% yield of homoveratrylamine along with 18% of the Pictet–Spengler cyclization product **5** derived from internal trapping of iminium ion **4**.



Hindered *N*-substituted 2-azanorbornenes readily undergo heterocycloreversion at ambient temperature (entries 7 and 8). For example, exposure of a 0.84 M aqueous solution of the azanorbornene derivative prepared from L-phenylalanyl-L-leucine methyl ester (entry 8) to 1.3 equiv of *N*-methylmaleimide at room temperature over a 4-h period gives rise to L-phenylalanyl-L-leucine methyl ester in 97% yield without any racemization.⁷ Similarly the azanorbornene derivative prepared from L-leucine methyl ester (entry 7) provided the parent amino acid as its methyl ester in 95% yield with no racemization.

Efforts are now focussed on investigating the synthetic potential and mechanistic implications of the heterocycloreversion reaction of azanorbornenes and related systems. The ability to efficiently incorporate a primary amino function into an azanorbornene by cyclocondensation of a simple *N*-alkyl iminium salt with cyclopentadiene in water, coupled with the facile retro aza Diels–Alder reaction described above, suggests that azanorbornenes may serve

(7) Any racemization that may accompany the transformations depicted in entries 7 and 8 is less than the detection limit which is estimated at 0.06–0.07% (Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Denkwalter, R. G.; Hirschmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 3254).

as useful new protecting groups for primary amines. Studies along these lines are currently underway.

Acknowledgment. This investigation was supported by a grant from the National Science Foundation. The 300-MHz NMR instrument (Varian XL-300) used in the above studies was purchased with funds provided by the National Institutes of Health. We are grateful to Dr. Scott Larsen for developing a practical synthesis of 2-azanorbornene.

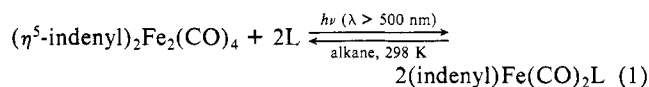
Photochemistry of $(\eta^5\text{-indenyl})_2\text{Fe}_2(\text{CO})_4$ in the Presence of $2e^-$ Donor Ligands: Reversible Formation of the Radicals $(\text{indenyl})\text{Fe}(\text{CO})_2\text{L}$

Yee-Min Wu, Chaofeng Zou, and Mark S. Wrighton*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received May 21, 1987

We report the photochemical reaction and the reverse thermal process represented by eq 1 for $L = \text{CO}$, PPh_3 , and PPh_2H . The



indenyl ligand can bind in either an η^5 or η^3 fashion,¹⁻³ and the facile, reversible "ring slippage", $\eta^5 \rightleftharpoons \eta^3$ binding, has been invoked to account for the greater substitution lability of η^5 -indenyl complexes compared to $\eta^5\text{-C}_5\text{H}_5$ complexes.¹⁻⁴ Ring slippage in a variety of $\eta^5\text{-C}_5\text{H}_5$ complexes and their derivatives has been invoked to account for a number of interesting chemical transformations.⁴ Recent work⁵ from this laboratory implicating reactions of CO and PPh_3 with photogenerated $(\text{C}_5\text{R}_5)\text{Fe}(\text{CO})_2$ ($R = \text{H, Me}$) stimulated us to investigate the photochemistry of $(\eta^5\text{-indenyl})_2\text{Fe}_2(\text{CO})_4$ with the hope of stabilizing the product from thermal reaction of CO and PPh_3 with photogenerated $(\text{indenyl})\text{Fe}(\text{CO})_2$ radicals. It should be noted that $(\eta^3\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{L}$ radicals are known⁶ and have been characterized by EPR and IR spectroscopy. The existence of $(\eta^3\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{L}$ ⁶ and the facile $\eta^5 \rightarrow \eta^3$ ring slippage of the indenyl ligand^{1,4} is consistent with the notion that $(\eta^3\text{-indenyl})\text{Fe}(\text{CO})_2\text{L}$ might be detectable. We note the recent isolation and X-ray crystal structural characterization of $[(\eta^3\text{-indenyl})\text{Fe}(\text{CO})_3]^-$ from re-

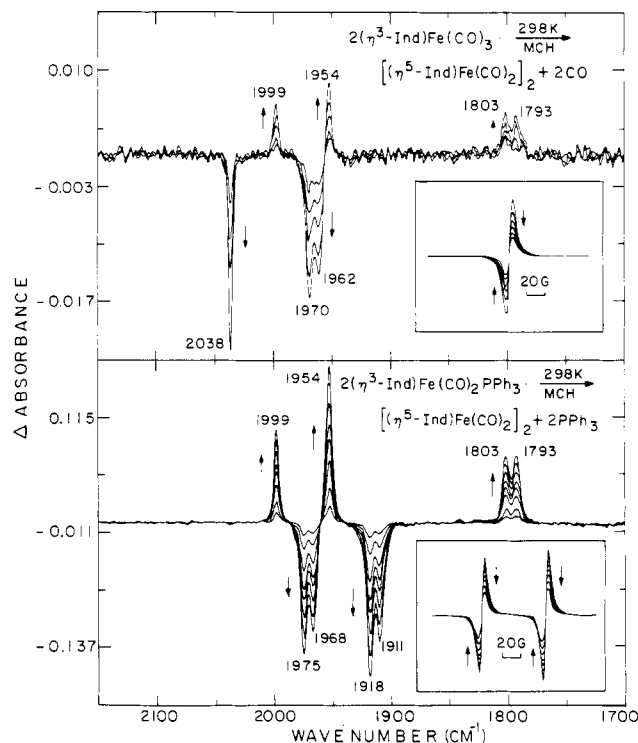
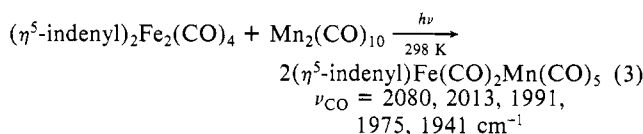
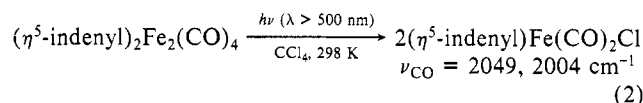


Figure 1. IR and EPR (independently prepared sample) spectral changes accompanying reaction of $(\text{indenyl})\text{Fe}(\text{CO})_2\text{L}$ to form $(\eta^5\text{-indenyl})_2\text{Fe}_2(\text{CO})_4$ (1999, 1954, 1803, 1793 cm^{-1}) in deoxygenated methylcyclohexane at 298 K. Data for $L = \text{CO}$ (top, cell path = 0.1 mm) are for a CO-saturated solution, and the timescale of the IR spectral changes is ~ 2 min. Data for $L = \text{PPh}_3$ (bottom, cell path = 1.0 mm) are for a solution containing 0.05 M PPh_3 , and the timescale of the IR spectral changes is ~ 10 min. The $(\text{indenyl})\text{Fe}(\text{CO})_2\text{L}$ radicals were formed by $\lambda > 500$ nm irradiation of $(\eta^5\text{-indenyl})_2\text{Fe}_2(\text{CO})_4$, and the final IR spectra shown in both cases represent $>99\%$ consumption of the photogenerated radical. The IR data are for initial $(\text{indenyl})\text{Fe}(\text{CO})_2\text{L}$ concentration of 0.35 and 0.40 mM for $L = \text{CO}$ and PPh_3 , respectively.

actions of CO with $[(\eta^5\text{-indenyl})\text{Fe}(\text{CO})_2]^-$.

Irradiation of $(\eta^5\text{-indenyl})_2\text{Fe}_2(\text{CO})_4$ ⁸ yields chemistry consistent with that for $(\eta^5\text{-C}_5\text{R}_5)_2\text{Fe}_2(\text{CO})_4$,⁹ both CO loss and Fe-Fe homolysis products can be detected, depending on conditions. Fe-Fe homolysis products result from photoexcitation of $(\eta^5\text{-indenyl})_2\text{Fe}_2(\text{CO})_4$ in fluid solution at 298 K, eq 2 and 3. The



photochemistry in the presence of CCl_4 is consistent with the

(7) Forschner, T. C.; Cutler, A. R.; Kulinging, R. K. *Organometallics* **1987**, *6*, 889.

(8) (a) Gansow, O. A.; Burke, A. R.; Vernon, W. D. *J. Am. Chem. Soc.* **1976**, *98*, 5817. (b) Forschner, T. C.; Cutler, A. R. *Inorg. Chim. Acta* **1985**, *102*, 113.

(9) (a) Meyer, T. J.; Caspar, J. V. *Chem. Rev.* **1985**, *85*, 187. (b) Hepp, A. F.; Blaha, J. P.; Lewis, C.; Wrighton, M. S. *Organometallics* **1984**, *3*, 174. (c) Blaha, J. P.; Bursten, B. E.; Dewan, J. C.; Frankel, R. B.; Randolph, C. L.; Wilson, B. A.; Wrighton, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 4561. (d) Hooker, R. A.; Rest, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1022. (e) Moore, B. K.; Simpson, M. B.; Poliakoff, M.; Turner, J. J. *J. Chem. Soc., Chem. Commun.* **1984**, 972. (f) Moore, B. D.; Poliakoff, M.; Turner, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 1819. (g) Dixon, A. J.; Healy, M. A.; Hodges, P. M.; Moore, B. D.; Poliakoff, M.; Simpson, M. B.; Turner, J. J.; West, M. A. *J. Chem. Soc., Faraday Trans.* **1986**, *82*, 2083. (h) Abrahamson, H. B.; Palazzotto, M. C.; Reichel, C. L.; Wrighton, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 4123.