An Efficient Photochemical Approach to the *trans*-Bicyclo[5.1.0]octene Ring System

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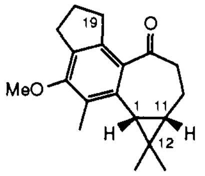
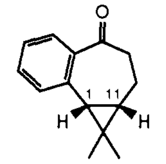
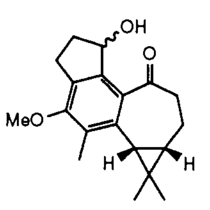
We report here the photochemical behavior of the closely related benzobicyclo[5.1.0]oct-2-en-4-ones **1** and **2**. Our initial objective in this area was the selective insertion of oxygen at C(19) of ketone **1**, to furnish advanced intermediate **3** for the synthesis of jatropholones A and B (**4** and **5**),[1] novel diterpenoids isolated from *Jatropha gossypiifolia L.* (*Euphorbiaceae*).[2]



(+)-**1**



(+)-**2**



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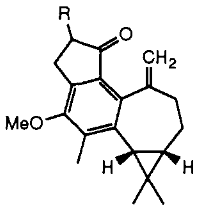
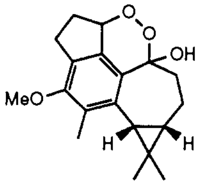


4 R = α-CH$_3$
5 R = β-CH$_3$

Based on literature precedent,[3] we envisioned that photoenolization of **1**, followed by capture of the highly reactive dienol with oxygen, would yield endoperoxide **6** or products derived therefrom.[4] Instead, irradiation of **1** in hexane saturated with oxygen afforded diketone **7**[5] as the only isolable product, in 40% yield, via scission of the peripheral benzylic cyclopropane bond. Although **7** was not useful vis-à-vis our jatropholone program, we were intrigued by the result in view of the known photochemical behavior of the parent bicyclo[5.1.0]oct-2-en-4-one, wherein the primary photochemical event is reported to involve cleavage of the central cyclopropyl bond.[6] Given the availability of enantiomerically enriched **1**[1] and **2** (vide infra), we elected to explore the photochemical behavior of these substrates.



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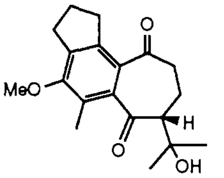

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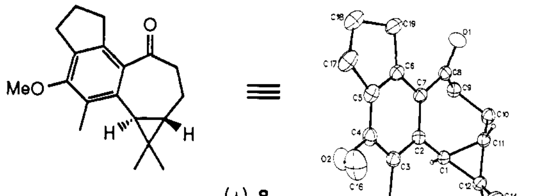
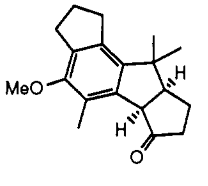
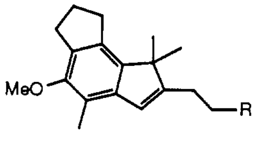
Irradiation of (+)-(1*R*,11*S*)-**1** (80% ee) in degassed hexane (0.07 M, 30 min, Pyrex)[7] led to a photochemical stationary state (ca. 4:1, trans:cis) from which the strained[8] trans isomer, (+)-(1*S*,11*S*)-**8**,[5] could be isolated in crystalline form [mp 124–125 °C, $[\alpha]^{19}_{D}$ +175° (*c* 0.40, CHCl$_3$)] in 68% yield (85% based on recovered **1**).[9-11] Diagnostic of the trans ring juncture was the upfield shift of the C(11)-methine multiplet in the ^{1}H NMR spectrum; confirmation was secured through the aegis of a single-crystal X-ray analysis.[12] Comparison of the UV spectra of **1** and **8** revealed no significant difference in either λ_{max} or ϵ for any of the observed absorbances. Interestingly, prolonged irradiation of either (+)-**1** or (+)-**8** (0.06 M, hexane, 6 h) led to ketone (+)-**9**[5] (30%) and aldehyde **10**[5] (6%), two secondary photoproducts arising via marked skeletal rearrangement. The structure of **10** was determined by X-ray analysis of the corresponding acid **11**,[5,13] whereas the structure of **9** was assigned on the basis of spectral properties in conjunction with its photochemical conversion to **10**.[16]



(+)-**8**



(+)-**9**



10 R = CHO
11 R = COOH

Importantly, a dramatic influence on both the stationary state and the secondary photochemistry was noted upon irradiation of **1** in the presence of the triplet quencher piperylene (mixture of isomers). With 0.5 and 5.0 equiv of diene, the equilibrium ratios increased to 8:1 and 50:1 (trans:cis) within 3 and 6 h, respectively;[14] neither **9** nor **10** could be detected in the latter experiment. Moreover, a preparative reaction (0.6 M hexane, 5.0 equiv of

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[1] Smith III, A. B.; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. N. *J. Org. Chem.* **1985**, *50*, 3239.

[2] Purushothaman, K. K.; Chandrasekharan, S.; Cameron, A. F.; Connolly, J. D.; Labbé, C.; Maltz, A.; Rycroft, D. S. *Tetrahedron Lett.* **1979**, 979.

[3] For a review of photoenolization, see: Sammes, P. G. *Tetrahedron* **1976**, *32*, 405.

[4] Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1845.

[5] The structure assigned to each new compound is in accord with its infrared and high field (500 or 250 MHz) ^{1}H NMR spectra as well as appropriate parent ion identification by high resolution mass spectrometry.

[6] Paquette, L. A.; Meehan, G. V.; Henzel, R. P.; Eizember, R. F. *J. Org. Chem.* **1973**, *38*, 3250.

[7] All irradiations were carried out with a 450-W Hanovia lamp (no. 679A0360) suspended in a Pyrex well cooled with tap water. Reaction mixtures were held adjacent to the well in Pyrex test tubes; for sensitized reactions a merry-go-round apparatus was employed.

[8] The difference in heats of formation for the parent *trans*- and *cis*-bicyclo[5.1.0]octanes is 12 ± 1 kcal/mol: Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312. Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109. A calorimetric study of bicyclo[5.1.0]octane derivatives substituted in the cyclopropane ring gave $\Delta H = -9.0 \pm 1.0$ kcal/mol for the trans-to-cis isomerization.[9b] The introduction of trigonal carbons as in **1**, **2**, **8**, and **14** is expected to further increase the strain energies of the trans compounds relative to the cis isomers; cf.: Wiberg, K. B.; Lupton, E. C., Jr.; Wasserman, D. J.; de Meijere, A.; Kass, S. R. *J. Am. Chem. Soc.* **1984**, *106*, 1740.

[9] (a) The 4:1 trans:cis ratio and the stability of **8** are particularly striking in view of the 48:52 photostationary state and product lability encountered in a similar *trans*-bicyclo[5.1.0]octane preparation.[9b] (b) Pirkle, W. H.; Lunsford, W. B. *J. Am. Chem. Soc.* **1972**, *94*, 7201. We thank a referee for bringing this paper to our attention.

[10] For a review of photochemical cis–trans isomerization of aryl- and vinylcyclopropanes, see: Hixson, S. S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1979; pp 191–260.

[11] For leading references to the preparation of other *trans*-bicyclo[n.1.0] ring systems, see: Ashe III, A. J. *Tetrahedron Lett.* **1969**, 523. Wiberg, K. B.; de Meijere, A. *Tetrahedron Lett.* **1969**, 519. Gassman, P. G.; Williams, F. J.; Seter, J. *J. Am. Chem. Soc.* **1968**, *90*, 6893. Gassman, P. G.; Bonser, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 667. Gassman, P. G.; Mlinarić-Majerski, K. *J. Org. Chem.* **1986**, *51*, 2398. Masamune, S.; Baker, P. M.; Hojo, K. *J. Chem. Soc., Chem. Commun.* **1969**, 1203.

[12] Carroll, P. J.; Liverton, N. J.; Smith III, A. B. *Acta Crystallogr.* **1986**, *C42*, 1594.

[13] Unpublished results of Dr. P. Carroll, Univeristy of Pennsylvania X-ray Crystallographic Facility.

[14] Ratios were determined by calibrated analytical HPLC and/or capillary GC.

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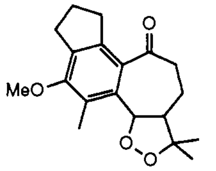
piperylene, 8 h, Pyrex) furnished (+)-**8** in 74% isolated yield, nearly double that obtained in the absence of quencher. Qualitatively, these observations indicate that the photochemical isomerizations of **8** proceed via the triplet manifold and that the initial cis-to-trans conversion must occur either via a triplet at a rate faster than diffusion or via a singlet excited state.[15]

A self-consistent mechanistic picture for the formation of **7–10** involves initial establishment of a photostationary state between **1** and **8**, via the intermediacy of a 1,3-diradical produced by rupture of the C(1,12) peripheral bond. In the presence of oxygen, diradical capture affords endoperoxide **12** (not observed); subsequent fragmentation would lead to **7**. Alternatively, in the absence of oxygen, the diradical rearranges to **13** (not observed), which in turn undergoes facile Norrish type I α-cleavage[16] to afford **9** and **10**.



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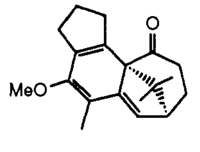

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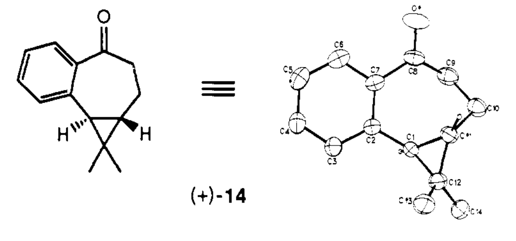
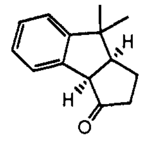
This scenario requires that the stereochemical integrity of the C(11) stereocenter be maintained. We explored this question by determining the enantiomeric purity of (+)-**9**, as obtained above; it proved to be 66% ee,[17] compared with 80% ee[18] for (+)-**1**. Thus, scission of the peripheral bond cannot be the sole pathway whereby the photostationary state is established. To ascertain the extent of peripheral versus central bond cleavage,[19] we turned to the simpler, more readily available ketone **2**.[20]

Initial photolyses, carried out with racemic **2**[5] in degassed hexane (0.09 M, 30 min, Pyrex), led to **14**[5] (mp 55–56 °C), isolated in 37% yield (93% based on recovered **2**). Assignment of the trans ring fusion again was initially based on ^{1}H NMR and then confirmed via X-ray analysis.[13] In contrast with the isomerization of **1**, irradiation of **2** produced a 1:1 photostationary state (trans:cis); subsequently (3 h), inefficient secondary photochemistry afforded **15**[5] and **16**[5] in 5% and 2% yields, respectively.[21] As before, piperylene substantially influenced both the stationary state and the secondary photoreactions. With 0.5 and 5.0 equiv of quencher, the equilibrium shifted to 4:1 and 7:1 (trans:cis); in the latter case (6 h photolysis), multigram amounts of **14** could be isolated in 68% yield, a 2.6-fold improvement over the control.[22]



(+)-14



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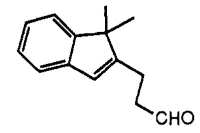

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Competition between central and peripheral bond cleavage during the cis-to-trans and trans-to-cis interconversions was investigated with enantiomerically enriched **2** and **14**. In the absence of piperylene, irradiation of (−)-(1*S*,11*R*)-**2** (90% ee)[23a] afforded (−)-(1*R*,11*R*)-**14** (78% ee),[24] whereas isomerization of (+)-(1*S*,11*S*)-**14** (93% ee)[23b] gave (+)-(1*R*,11*S*)-**2** (72% ee).[24] These results indicate that scission of the peripheral bond was operative in 87% of the cis-to-trans conversions but only in 77% of the reverse reactions.[25] The latter increase in central σ-bond cleavage may

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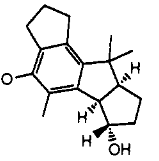
(15) For discussion of singlet and triplet reactivities in related reactions, see: (a) Hixson, S. S.; Borovsky, J. *J. Am. Chem. Soc.* **1976**, *98*, 2840. (b) References 6 and 10.

(16) For a review of Norrish type I cleavage, see: Chapman, O. L.; Weiss, D. S. In *Organic Photochemistry*; Chapman, O., Ed.; Marcel Dekker: New York, 1973; pp 241–250.

(17) (a) Determined via ^{1}H NMR analysis (C_6D_6 solvent) of the Mosher esters[17b] prepared from alcohol **17**,[5] the more polar epimer obtained upon $NaBH_4$ reduction of **9**. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.



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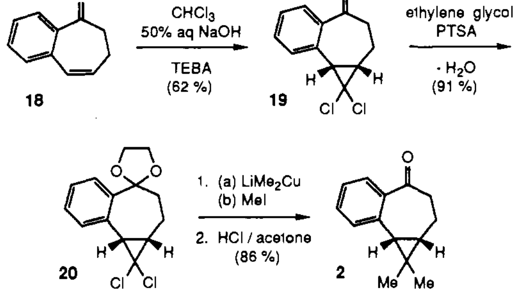
(18) Determined via HPLC using Daicel Industries Chiralpak OT (+) column.

(19) Preferential reaction of the C(1,12) peripheral bond is in accord with diradical stability considerations, which also suggest that cleavage of the C(11,12) peripheral bond is strongly disfavored. Investigation of a substrate lacking cyclopropane methyl groups is planned.

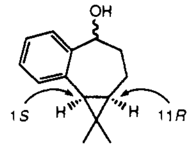
(20) Prepared in four steps (48% overall yield) from the known benzosuberenone **18** as outlined below. For the preparation of **18**, see: Buchanan, G. L.; Lockhart, D. R. *J. Chem. Soc.* **1959**, 3586.



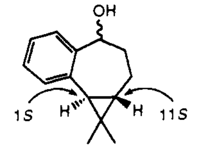
(21) A third compound, the structure of which has yet to be fully delineated, comprised 9% of the isolated material.

(22) As noted earlier for **1** and **8**, the UV spectra of **2** and **14** did not differ significantly.

(23) (a) Sodium borohydride reduction of (±)-**2** gave an inseparable mixture of alcohols **21**[5] and **22**[5] (2.2:1). Conversion to the corresponding (*S*)-*O*-methylmandelate esters, flash chromatography, and methanolysis (sodium methoxide, methanol, 25 °C) then furnished (+)- and (−)-**21**. The assignment of the relative stereochemistry of **21** was based upon previous work in our laboratory: Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith III, A. B. *J. Org. Chem.* **1982**, *47*, 3960. The absolute configurations [(1*S*,11*R*) for (−)-**21**] were determined via the Trost NMR method for analysis of the *O*-methylmandelate derivatives: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. The enantiomeric purity of (−)-**21** was determined by ^{1}H NMR analysis ($CDCl_3$) of the derived Mosher esters.[17b] Jones oxidation (acetone, 25 °C) of (+)- and (−)-**21** then furnished (+)- and (−)-**2**, respectively. (b) Sodium borohydride reduction of (±)-**14** afforded alcohols **23**[5] and **24**[5] (1:2) after chromatography. The major epimer **24** was resolved via flash chromatography of the (*S*)-*O*-methylmandelate esters, followed by methanolysis as above. The assignment of relative stereochemistry of **24** was based on NOE experiments, and the absolute configurations [(1*S*,11*S*)- for (+)-**24**] were again established by NMR analysis of the *O*-methylmandelates. The enantiomeric purity of (+)-**24** was determined via ^{1}H NMR analysis ($CDCl_3$) of the corresponding Mosher esters.[17b] Oxidation as above then converted (+)- and (−)-**24** to (+)- and (−)-**14**, respectively.



(−)-**21** β-OH
22 α-OH



23 α-OH
(+)-**24** β-OH

(24) Product formation was monitored by HPLC on a column containing a homochiral stationary phase. The observed enantiomeric purity was then extrapolated to low conversion (ca. 1–2%). The cis enantiomers (**2**) were analyzed using Daicel Industries Chiralcel OC column, whereas the Chiralpak OT (+) column was employed for analysis of the trans enantiomers (**14**).

reflect improved overlap of the central bond with the aromatic π-system,[26] as well as weakening of this bond,[27] in the trans compound.

In summary, we have uncovered a remarkably efficient photochemical route to the strained *trans*-bicyclo[5.1.0]octene ring system. Efforts to synthesize theoretically interesting unnatural products via extensions of this approach are underway in our laboratory.

Acknowledgment. Support for this work was provided by the National Institutes of Health (National Cancer Institute) through Grant 22807.

Registry No. (+)-**1**, 101836-56-0; (+)-**2**, 120666-81-1; (−)-**2**, 120710-33-0; (±)-**2**, 120710-31-8; (−)-**7**, 120666-82-2; (+)-**8**, 105990-58-7; (+)-**9**, 120666-83-3; **10**, 120666-84-4; **11**, 120666-85-5; (+)-**14**, 120710-35-2; (−)-**14**, 120710-34-1; (±)-**14**, 120710-32-9; (±)-**15**, 120666-86-6; **16**, 120666-87-7.

Supplementary Material Available: Spectroscopic data (IR, UV, ^{1}H NMR, ^{13}C NMR, and HRMS) for **2**, **7–11**, **14–16** (3 pages). Ordering information is given on any current masthead page.

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(25) In isomerizations involving central bond cleavage, radical inversions at C(1) and C(11) were assumed to be equally probable.

(26) For pertinent discussion, see ref 15a and 10.

(27) See, for example: Gassman, P. G.; Bonser, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 667.

A Dinucleating Hexaimidazole Ligand and Its Dicopper(II) Methanol Inclusion Complex

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Notable progress has been made using dinucleating ligands to model features of Cu_2 cores in hemocyanin and tyrosinase[1-3] and of Fe_2 centers in iron-oxo proteins[4] such as semimethemerythrin.[5] Little work has yet been reported with polyimidazole ligands,[6] however, and none with dinucleating species containing imidazoles as the sole N-donors. Application of the latter class to mimic the chemical and physical properties of dinuclear metalloproteins with histidine-dominated cores could ultimately prove to be as important as using porphyrins, rather than other tetraaza macrocycles, in biomimetic heme research.

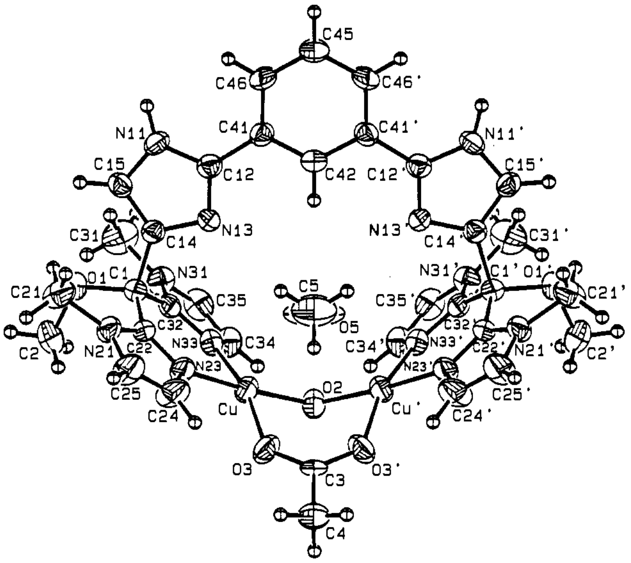
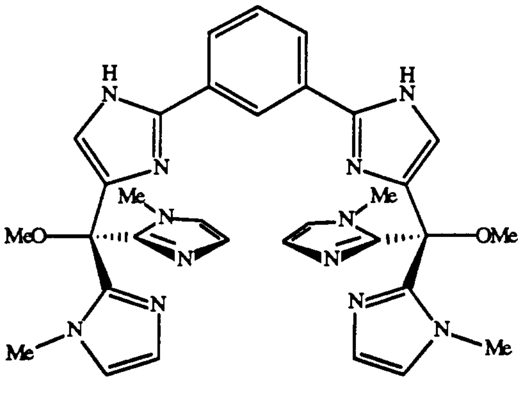


Figure 1. ORTEP drawing of **2**·1.5THF·MeOH showing the 40% probability thermal ellipsoids and atom labels for all non-hydrogen atoms (excluding the perchlorate counterions and THF solvate molecules). Selected interatomic distances (Å) and angles (deg) are as follows: Cu–O(2), 1.934 (5); Cu–O(3), 1.937 (7); Cu–N(23), 1.973 (8); Cu–N(33), 1.979 (8); Cu···Cu′, 3.156 (3); Cu···N(13), 4.132 (8); Cu–O(2)–Cu′, 109.3 (4); O(3)–Cu–O(2), 91.6 (4); O(3)–Cu–N(23), 87.9 (3); N(23)–Cu–N(33), 89.1 (3); N(33)–Cu–O(2), 92.7 (4).

In this communication we wish to report the synthesis of hexaimidazole **1**, a molecule specifically designed to encapsulate two metals in a biomimetic environment. In particular, **1** is preorganized to inhibit formation of undesired polynuclear species, an outcome previously encountered in attempts to prepare dimetallic complexes using multidentate N-donor ligands lacking a coordinating bridge atom.[7] As proof of its dinucleating ability, we present the synthesis, X-ray crystal structure, and physical characterization of a dicopper(II) complex of **1** which, as an added feature of interest, contains an included methanol.



1

Compound **1** was obtained upon dual metalation (potassium diisopropylamide)[8] at C5 of the N-protected imidazoles in a 1,3-bis(2-imidazolyl)benzene[9,10] followed by condensation with

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(1) (a) Karlin, K. D.; Cruse, R. W.; Gultneh, Y.; Farooq, A.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1987**, *109*, 2668. (b) Karlin, K. D.; Haka, M. S.; Cruse, R. W.; Meyer, G. J.; Farooq, A.; Gultneh, Y.; Hayes, J. C.; Zubieta, J. *Ibid.* **1988**, *110*, 1196. (c) Cruse, R. W.; Kaderli, S.; Karlin, K. D.; Zuberbühler, A. D. *Ibid.* **1988**, *110*, 6882.

(2) (a) Sorrell, T. N.; O'Connor, C. J.; Anderson, O. P.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1985**, *107*, 4199. (b) Review: Sorrell, T. N. *Tetrahedron* **1989**, *45*, 3.

(3) McKee, V.; Zvagulis, M.; Dadgegian, J. V.; Patch, M. G.; Reed, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 4765.

(4) Review: Lippard, S. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 344.

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