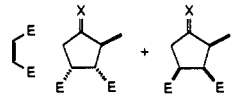
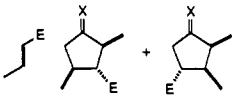
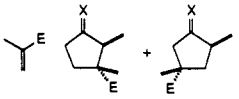
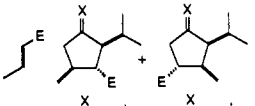
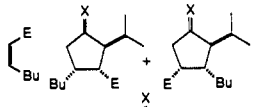
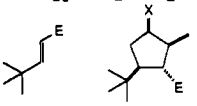
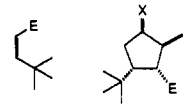
Table I. Regio- and Stereoselective [3 + 2] Cycloaddition[a]

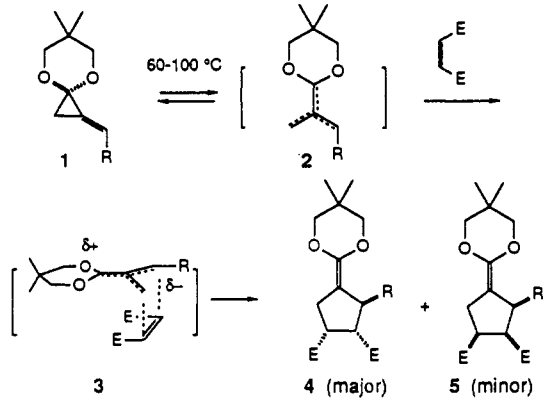
entry	olefin	cycloadducts[b] (E = COOMe, X = C(OCH$_2$CMe$_2$CH$_2$O))	solvent[c]	%yield (product ratio)
1	1a		octane (1.9)	77 (97:3)
			benzene (2.3)	88 (95:5)
			toluene (2.6)	86 (97:3)
			DME (7.2)	85 (92:8)
			ClCH$_2$CH$_2$Cl (10.4)	74 (92:8)
			DMF (36.7)	72 (80:20)
			acetonitrile (37.5)	78 (80:20)
			DMSO-d6 (46.6)	73 (73:27)
2	1a		toluene	81 (50:50)
3	1a		toluene	72 (1:1)
4	1b		CD_3CN	71 (96:4)
5	1b		CD_3CN	80 (1:1)
6	1a		CD_3CN	89 (>97:3)
7	1a		CD_3CN	not detected

[a] The reactions were carried out at 100–120 °C for 55–75 h under nitrogen except in entries 1 and 2 (80 °C, 20–35 h). The yields are based on pure isolated products after hydrolysis of the ketene acetals except in entries 2, 5, and 7, where they are based on NMR analysis. The product ratios were determined by capillary GC analysis on OV-1 or on OV-17. [b] In entry 5, X = C(OCH$_2$CH$_2$CH$_2$O). [c] The dielectric constants are for protio solvents: Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972.

even in a very polar solvent (cf. entries 4 and 6). Finally, we note that hydrolysis of the ketene acetal to the corresponding ester proceeds with high stereoselectivity (generally >90%). Thus, the cycloaddition and hydrolysis set four stereogenic centers with excellent stereocontrol.[10]

In summary, we have found a general, stereospecific, regio- and stereoselective thermal [3 + 2] cycloaddition reaction involving a 6π-electron transition state. The observed levels of selectivities may be better than those of its [4 + 2] counterpart, the uncatalyzed Diels–Alder reaction, and the reaction is unique among known all-carbon [3 + 2] cycloadditions.[1,2,11] Mechanistic and synthetic studies continue in these laboratories.

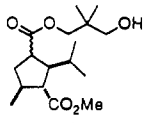
Scheme I



Acknowledgment. We thank the Ministry of Education, Science, and Culture of Japan and the Yamada Science Foundation for financial support.

Supplementary Material Available: Listings of experimental procedures, physical properties of the cycloadducts, and stereochemical assignments (17 pages). Ordering information is given on any current masthead page.

(10) Typical reaction procedure: Isopropylidenecyclopropane **1b** and methyl crotonate (1.1 equiv) in CD_3CN (0.5 mL/mmol of **1b**) were heated in a sealed tube at 100–120 °C for 50 h (>97% pure by capillary GC analysis). Careful NMR analysis indicated the regioisomeric ratio to be 96:4. Hydrolysis of the crude product (addition of 40 μL of 10% v/v aqueous AcOH) followed by purification on silica gel afforded a 95:3:2 isomeric mixture of cyclopentanecarboxylic acid ester i in 71% yield. This isomeric ratio indicates that the hydrolysis proceeded with >30:1 selectivity. The cycloaddition reaction is remarkably insensitive to the reaction conditions, and the acetals derived from neopentyl glycol and 1,3-propanediol (Table I, entry 5) may be employed with equal success.



i

(11) There is one previous report of endo-selective thermal [3 + 2] cycloaddition of TMM (with 3:1 selectivity): Little, L. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* **1979**, 305.

Photochemistry of α-Keto Phosphate Esters: Photorelease of a Caged cAMP

Richard S. Givens,* Phillip S. Athey, L. William Kueper III, Bogdan Matuszewski, and Jie-you Xue

Department of Chemistry
The University of Kansas
Lawrence, Kansas 66045

Received June 29, 1992

We report our results on a phosphate photoprotecting (or *cage*) group that rapidly releases phosphate ($k_r > 10^8$ s^{-1}) in nearly quantitative yield by efficient photolysis of the *caged* phosphate. As a demonstration of this strategy, cAMP was generated with an efficiency of 34% and a first-order rate constant of 3×10^8 s^{-1} by irradiation of benzoin cAMP, a caged nucleotide.

The recent interest in *caged* phosphates as precursors capable of rapid release of nucleotides and other biologically active phosphates to study the kinetics of muscle action by ATP,[1] calcium channel activation by GTP,[2] and visual excitation by the inositol phosphate cascade[3] has drawn attention to the need for better photolabile groups.[4] To date, the most commonly chosen *cage*

(1) (a) Arner, A.; Goody, R. S.; Rapp, G.; Ruegg, J. C. *J. Muscle Res. Cell Motil.* **1987**, *8*, 377–385. (b) Somlyo, A. V.; Goldman, Y. E.; Fujimori, T.; Bond, M.; Trentham, D. R.; Somlyo, A. P. *J. Gen. Physiol.* **1988**, *91*, 165–192. (c) McCray, J. A.; Trentham, D. R. *Annu. Rev. Biophys. Biophys. Chem.* **1989**, *18*, 239–270. (d) Kuhn, H.; Tewes, A.; Gagelmann, M.; Guth, K.; Arner, A.; Ruegg, J. C. *Pfluegers Arch.* **1990**, *416*, 512–518.

(2) Dolphin, A. C.; Wootton, J. F.; Scott, R. H.; Trentham, D. R. *Pfluegers Arch.* **1988**, *411*, 628–636.

(3) (a) Frank, T. M.; Fein, A. *J. Gen. Physiol.* **1991**, *97*, 697–723. (b) Walker, J. W.; Feeney, J.; Trentham, D. R. *Biochemistry* **1989**, *28*, 3272–3280.

(4) (a) Engels, J.; Schlaeger, E. *J. Med. Chem.* **1977**, *20*, 907; *Experientia* **1978**, *34*, 14–15. (b) Nerbonne, J. M.; Richard, S.; Nargeot, J.; Lester, H. A. *Nature* **1984**, *310*, 74. (c) Nargeot, J.; Nerbonne, J. M.; Engels, J.; Lester, H. A. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2395. (d) Kaplan, J. H.; Forbush, B.; Hoffman, J. B. *Biochemistry* **1978**, *17*, 1929. (e) McCray, J. A.; Trentham, D. R.; Reid, G. P.; Walker, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 7170. (f) McCray, J. A.; Trentham, D. R. *Annu. Rev. Biophys. Chem.* **1989**, *18*, 239.

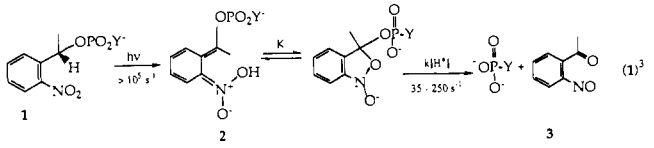
0002-7863/92/1514-8708$03.00/0

Table I. Quantum Efficiencies (Φ)[a] for Photolysis of Benzoin Phosphate Esters **4a–c** at 350 nm

ester 4	solvent	pH	Φ_{dis}[b]	Φ_{app}[b]	Φ'_{app}[c]
4a	C_6H_6	*d*	0.28	0.26	*d*
4b	H_2O/CH_3CN[e]	2.0	0.37	0.20	0.12
4b	H_2O/CH_3CN[e,f]	7.0	*d*	0.07	0.013
4c	H_2O/CH_3CN[e]	2.0	0.38	0.14	0.15
4c	H_2O/CH_3CN[e,f]	7.0	*d*	0.08	0.01

[a] Disappearance of **4a–c** and appearance of **5** and **6**. [b] Φ_{dis} = disappearance of **4**, and Φ_{app} = appearance of **5**. [c] Φ'_{app} = appearance of **6**. [d] Not determined. [e] H_2O/CH_3CN = 3:2. [f] ^{31}P NMR indicated rapid disappearance, but no other products were detected.

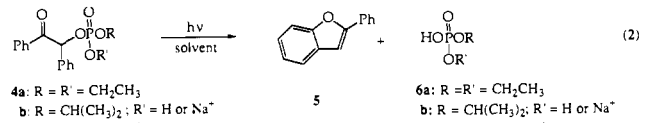
is the *o*-nitrobenzyl moiety **1**, which as an ester ligand on the phosphate function, e.g., P^3 of ATP, inhibits biological activity of the nucleotide. Photolysis (eq 1) releases the nucleotide, which is now free to exert its normal biological action.[4]



(1)[3]

Study of the subsequent biological process is hampered, however, by two inconvenient features of *o*-nitrobenzyl photochemistry: (1) the release of the phosphate occurs by a slow, rate-limiting hydrolysis ($k_r = 10^2\ s^{-1}$) of the *aci*-nitro intermediate **2**,[4e] and (2) the nitrosophenyl ketone **3** is not biologically inert.[4f]

Earlier we reported[5] that benzoin diethyl phosphate (**4a**) is efficiently converted to 2-phenylbenzo[*b*]furan upon photolysis in methanol, acetonitrile, or benzene. We now add our studies on the aqueous soluble derivatives, benzoin isopropyl phosphate (**4b**) and benzoin phosphate (**4c**).[6,7] Both of these esters, when irradiated in 60% aqueous acetonitrile at 350 nm, gave 2-phenylbenzo[*b*]furan (**5**) and the released phosphate (eq 2). The



(2)

4a: R = R' = CH_2CH_3
b: R = $CH(CH_3)_2$; R' = H or Na^+
c: R = R' = H or Na^+

5

6a: R = R' = CH_2CH_3
b: R = $CH(CH_3)_2$; R' = H or Na^+
c: R = R' = H or Na^+

efficiencies for disappearance of **4a–c** and appearance of furan **5** and phosphates **6a–c** (Table I) are pH dependent and highest under acidic conditions. Both reactions are quenched by sodium naphthalenesulfonate (E_T = 62 kcal/mol), indicating triplet-state reactivity. Triplet lifetimes of 2 and 4 ns,[8] respectively, were determined from Stern–Volmer quenching plots. The benzoin esters also gave quenchable phosphorescence emissions and displayed 0,0 bands at 395 ± 5 nm for E_T = 73.3 ± 0.9 kcal/mol.[9]

The concept that benzoin could serve as a cage for nucleotides[5a,6] was reduced to practice with the synthesis of benzoin cAMP (**7**).[10]

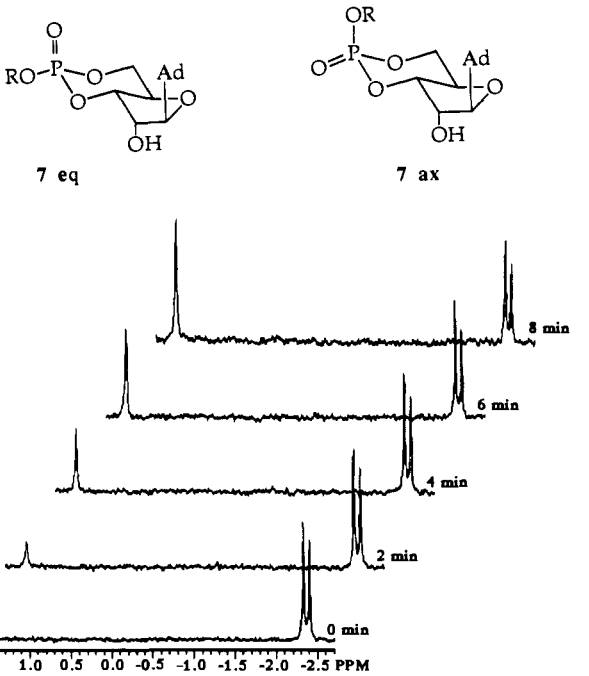


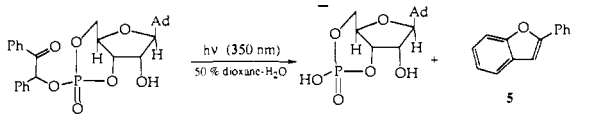
Figure 1. ^{31}P NMR (121.4 MHz; Varian XL-300, heteronuclear decoupled, 1024 transients) of the irradiation at 350 nm of benzoin cAMP (δ −2.36 (7 ax) and −2.28 ppm (7 eq)) releasing cAMP **8** (δ 1.73 ppm, s) as a function of irradiation time. (Ad = adenine.) See Table II for conditions.

Table II. Quantum Efficiencies (Φ)[a] for Photolysis of Benzoin Adenosine Cyclic 3′,5′-Monophosphate (**7**) at 350 nm in 1:1 Aqueous Buffer/Dioxane

aqueous buffer	pH	Φ_{dis}[b]	Φ_{app}[b]	Φ_{app}[c]
Tris (D_2O)	7.3	0.39	0.34	0.19
Tris (H_2O)	7.3	0.37	0.34	0.17
phosphate (D_2O)	8.4	*d*	*d*	0.17
phosphate (H_2O)	8.4	*d*	*d*	0.17
perchloric (D_2O)	1.6	0.40	0.36	0.16

[a] Disappearance of **7** and appearance of **5** and **8**. [b] Φ_{dis} = disappearance of **7**, and Φ_{app} = appearance of **8**. [c] Φ_{app} = appearance of **5**. [d] The Φ_{dis} or Φ_{app} could not be measured due to the interference of the ^{31}P signal from the buffer.

Irradiation of **7** in 1:1 dioxane/aqueous buffer at 350 nm (eq 3) generated cAMP exclusively, free of other phosphates as shown in the ^{31}P NMR spectra in Figure 1. The 2-phenylbenzo[*b*]furan



(3)

and cAMP were confirmed by HPLC and ^{31}P, ^1H, and ^{13}C NMR analysis of the photolysis mixture. As anticipated for phosphotriesters,[5b] the efficiency of this reaction was *not* pH dependent (Table II). This reaction, like the reactions of the model esters, was quenched by naphthalenesulfonate, affording a calculated triplet lifetime of 1 ns from the slope of a Stern–Volmer plot.[8]

No long-lived intermediates have been detected in the photochemistry of these and other phosphates we have examined.[5] Thus, direct photolysis of the C–O bond of the ester appears to be a likely mechanism.[5,11,12] From the quantum efficiency and the triplet

(5) (a) Givens, R. S.; Matuszewski, B. *J. Am. Chem. Soc.* **1984**, *106*, 6860. (b) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W., III; Xue, J.-y.; Fister, T. Unpublished work, manuscript in preparation. (c) Pincock, J. A.; Arnold, B.; Jurgens, A. *Can. J. Chem.* **1985**, *63*, 3140.

(6) (a) Baldwin et al. reported the photoactivated release of P_i phosphate from α-hydroxyacetophenone and benzoin phosphates (Baldwin, J. E.; McConnaughie, A. W.; Moloney, M. G.; Pratt, A. J.; Shim, S. B. *Tetrahedron* **1990**, *46*, 6879–6884). The organic products were not determined, however. An abstract has appeared on the use of 3,5-dimethoxybenzoin phosphate ester of ATP (Trentham, D. R.; Corrie, J. E. T.; Reid, G. P. *Biophys. J.* **1992**, *61*, A295). (b) Corrie, J. E. T.; Trentham, D. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2409–2417.

(7) The synthesis of phosphate mono- and diesters will appear in our full paper. The synthesis of mixed esters of benzoin phosphate was designed on the synthesis of mixed acetoin esters developed by Rameriz and Marecek (Rameriz, F.; Marecek, J. F. *Synthesis* **1985**, 449). 4,5-Diphenyl-2-oxido-2-oxo-1,3,2-dioxaphosphole (from benzil and $(CH_3O)_3P$) was converted to the mixed mono-, di-, and triesters of benzoin phosphate using the Rameriz procedure.

(8) Quenching rate constants for diffusion in 60% aqueous acetonitrile and in 50% aqueous dioxane were estimated to be 1.1 and 4.4 × $10^{10}\ M^{-1}\ s^{-1}$, respectively. (Murov, S. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1973; p 55.)

(9) Spectra were obtained in ether/isopentane/ethanol (5:5:2 v/v/v) at 77 K, excitation 360 nm.

(10) The *caged* benzoin cAMP was synthesized by an S_N2 displacement of tri-*n*-butylammonium cAMP on desyl bromide.[5,7]

(11) Studies by others[5c] and ourselves[5a,b,12] on naphthylmethyl and benzyl phosphates have shown that these reactions proceed through an ion pair intermediate. Recent results with 9-fluorenyl diethyl phosphate indicate that the 9-fluorenyl carbocation is formed in less than 25 ps after excitation with 30-ps pulse excitation at 266 nm and 23 °C in trifluoroethanol (E. Hilinski and J. H. Qian, private communication).

lifetime, a calculated rate constant of 3×10^8 s^{-1} was determined for the reaction of **7**. Similar values are derived from the results with **4a-c**.[5]

The photolytic reactions of benzoin phosphates yield a relatively stable, inert rearrangement product and released phosphate with rate constants of 10^8 s^{-1}, much higher than the rate constants reported for the *o*-nitrophenyl cage.[4e,f] We are further pursuing this general approach to *cage* ligands.

Acknowledgment. Support of this research by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Kansas General Research Fund is gratefully acknowledged.

(12) (a) Givens, R. S.; Matuszewski, B.; Athey, P. S.; Stoner, R. M. *J. Am. Chem. Soc.* **1990**, *112*, 6016. (b) Givens, R. S.; Singh, R. *Tetrahedron Lett.* **1991**, *32*, 7013.

Activation of Organic Carbonyl Compounds by Lewis Acids: Relative Reactivities of σ and π Adducts toward Nucleophiles and Implications for Enantioselective Addition Reactions

Darryl P. Klein and J. A. Gladysz*

Department of Chemistry
University of Utah
Salt Lake City, Utah 84112

Received March 31, 1992

A variety of protocols for enantioselective additions to aldehyes and ketones have now been developed.[1] These usually involve intermediate Lewis acid adducts, for which a multitude of potentially reactive binding motifs are possible.[2] Thus, little is known regarding mechanisms of enantioselection, and similar ambiguities attend other Lewis acid mediated reactions of organic carbonyl compounds.[3] We have undertaken a detailed study of complexes of the chiral rhenium Lewis acid $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ with aldehydes and ketones. This has included the structural characterization of, and diastereoselective hydride and cyanide additions to, both π and σ adducts.[4-6] In this communication, we report the first determination of the relative reactivity of π and σ isomers of Lewis acid/O=CRR′ complexes toward nucleophiles.

The previously reported pentafluorobenzaldehyde complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}CHC_6F_5)]^+BF_4^-$ (**1a**) shows no detectable amount of a σ isomer in CH_2Cl_2 at 26 °C by IR or UV/visible spectroscopy,[5a] and π/σ ratios for these compounds further increase upon cooling. Complex **1a** exists as a 98:2 mixture of two configurational diastereomers, $\mathbf{1a}_\pi$ and $\mathbf{1a}_{\pi'}$ (Scheme I),[7]

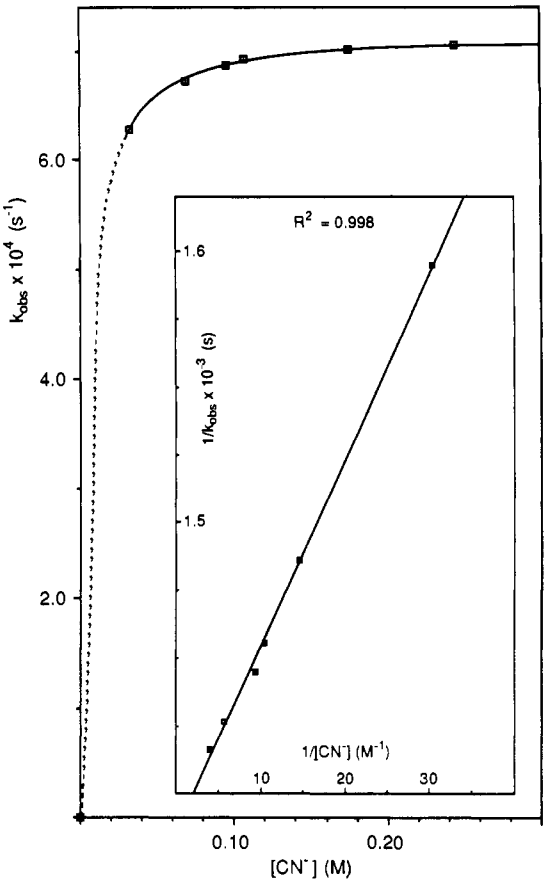
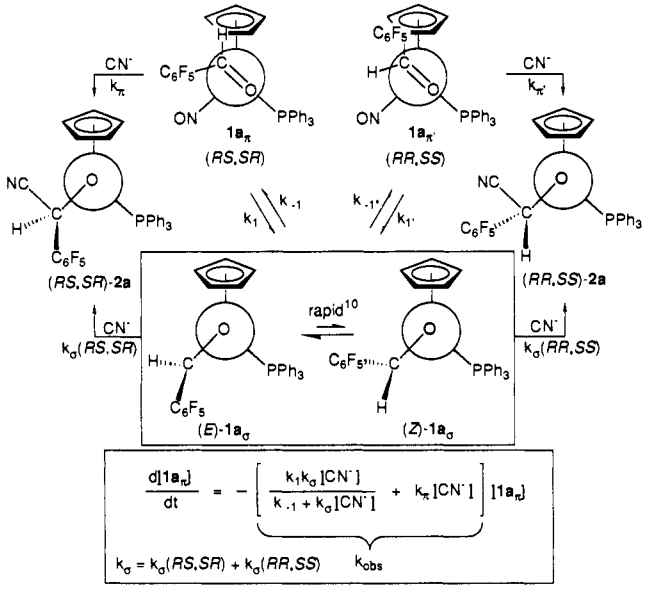


Figure 1. Plot of k_{obs} vs [CN^-] and (inset) $1/k_{obs}$ vs $1/[CN^-]$ for the reaction of (RS,SR)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}CHC_6F_5)]^+BF_4^-$ ($\mathbf{1a}_\pi$) and PPN^+CN^- in $CDCl_2F$ at −83 °C ([CN^-] > [$\mathbf{1a}_\pi$]).

Scheme I. Possible Pathways for CN^- Addition to Pentafluorobenzaldehyde Complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}CHC_6F_5)]^+BF_4^-$ (**1a**)



which slowly interconvert via σ isomers $\mathbf{1a}_\sigma$ ($\Delta G^\ddagger_{300K} \geq 15$ kcal/mol).[5b] The reaction of $\mathbf{1a}_\pi$ and PPN^+CN^- was monitored by ^{31}P NMR spectroscopy ($CDCl_2F$, −83 °C) under pseudo-first-order conditions ([CN^-] > [$\mathbf{1a}_\pi$]). Rate data are summarized

(1) Lead references to an extensive literature: (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321. (c) Singh, V. K. *Synthesis* **1992**, 605.

(2) Theoretical studies: (a) LePage, T. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 6642. (b) Branchadell, V.; Oliva, A. *J. Am. Chem. Soc.* **1991**, *113*, 4132. (c) Nevalainen, V. *Tetrahedron: Asymmetry* **1991**, *2*, 1133.

(3) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1991**, *113*, 8973; **1992**, *114*, 4536.

(4) (a) Garner, C. M.; Quirós Méndez, N.; Kowalczyk, J. J.; Fernández, J. M.; Emerson, K.; Larsen, R. D.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 5146. (b) Dalton, D. M.; Fernández, J. M.; Emerson, K.; Larsen, R. D.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9198. (c) Agbossou, F.; Ramsden, J. A.; Huang, Y.-H.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1992**, *11*, 693.

(5) (a) Quirós Méndez, N.; Arif, A. M.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1473. (b) Quirós Méndez, N.; Mayne, C. L.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1475. (c) Klein, D. P.; Dalton, D. M.; Quirós Méndez, N.; Arif, A. M.; Gladysz, J. A. *J. Organomet. Chem.* **1991**, *412*, C7.

(6) Dalton, D. M.; Garner, C. M.; Fernández, J. M.; Gladysz, J A. *J. Org. Chem.* **1991**, *56*, 6823.

(7) The π/π' ratios are not temperature dependent: Quirós Méndez, N. Ph.D. Thesis, University of Utah, 1991. The error limits on all integer ratios in this paper are ±2 (e.g., 50:50 ≡ (50 ± 2):(50 ± 2)).

0002-7863/92/1514-8710$03.00/0