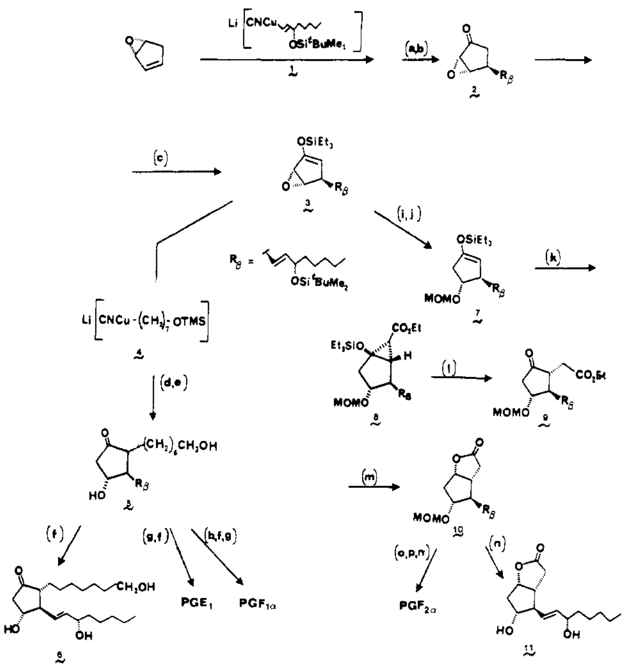
Scheme I[a]



[a] Reagents: (a) t-BuOOH, VO(acac)$_2$, PhH; (b) CrO$_3$·pyridine, CH$_2$Cl$_2$; (c) LDA, THF, -78 °C; then Et$_3$SiCl; (d) 4.0 equiv of 4, Et$_2$O, -78 °C → rt; (e) 1.3 equiv of KF, pH 7 phosphate buffer, EtOH; (f) HF, CH$_3$CN; (g) O$_2$, PtO$_2$, H$_2$O-acetone; (h) L-Selectride, THF, 0 °C; (i) LiAlH$_4$, Et$_2$O; (j) CH$_3$OCH$_2$Cl, i-Pr$_2$EtN, CH$_2$Cl$_2$; (k) EtO$_2$C-CHN$_2$, CuSO$_4$ (cat.), PhH, 90 °C; (l) Et$_3$NF, THF, rt; (m) PBPH, THF, -78 °C → rt; (n) 24% aqueous HBr, DME; (o) Dibal-H, CH$_2$Cl$_2$, -78 °C; (p) Na$^+$ [Ph$_3$P=CH-(CH$_2$)$_3$CO$_2^-$], PhH-Me$_2$SO, 75 °C.

pecific alkylation of 7 was unsuccessful and led to enolate equilibration and β-elimination of the protected 11-hydroxyl group.[13] The selective carbene addition onto the C8–C9 double bond, therefore, was devised as an indirect route, since such a reaction would render a (silyloxy)-substituted cyclopropane that could then be fragmented to generate the corresponding α-alkylated cyclopentanone.[14] Examination of models suggested that the carbene addition would preferentially take place from the α-side of the molecule (i.e., trans to the β-chain), setting up the correct stereochemistry at C8. Thus, reaction of 7 with ethyl diazoacetate in the presence of a catalytic amount of CuSO$_4$ gave 8 (70%) as a 4:1 mixture of exo and endo isomers, respectively.[15] Treatment of this mixture with triethylammonium fluoride effected selective desilylation of the triethylsilyl group and regiospecific opening of the cyclopropane ring to afford γ-keto ester 9 (95%) as the only product.[16] Reduction of the cyclopentanone carbonyl from the β-face of the molecule with lithium *cis,cis,trans*-perhydro-9b-boraphenalyl hydride (PBPH)[17] in THF at -78 °C, followed by warming of the resulting alkoxy ester solution, resulted in the formation of lactone **10** (80%). Removal of the protecting groups could be achieved simultaneously with 24% aqueous HBr in dimethoxyethane,[18] or, sequentially, by first removing the *tert*-butyldimethylsilyl group with 15% aqueous HF in acetonitrile[9] and then the methoxymethylene group with 5% HCl in aqueous THF. Chromatographic separation provided the known[19] lactone **11** (and its C15-epimer) in 30–40% overall yield from **2**. A conclusive proof of their structures was obtained by converting the hydroxy-protected lactone **10** into (±)-PGF$_{2\alpha}$[11] (and its C15-epimer) via reaction of the corresponding lactol with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide[20] and subsequent removal of the protecting groups.

In summary, the successful synthesis of PGE$_1$ and PGF$_{1\alpha}$ in less than ten steps from cyclopentadiene monoepoxide amply demonstrates the synthetic utility of the strategy involving a tandem 1,4-addition of cyanocuprates. The cyclopropanation approach, on the other hand, leads to a Corey lactone bearing a fully functionalized β-chain, which allows the synthesis of prostaglandins of the 2-series and many of their analogues.

Acknowledgment. The initial phase of this research was supported by NIH (CA22237). We acknowledge NFS for partial support of a Brüker WM-360 FT NMR spectrometer. We also thank Dr. Douglas R. Morton of The Upjohn Company for providing us with samples of pure 1-decarboxy-1-hydroxymethyl PGE$_1$, PGF$_{1\alpha}$, and PGF$_{2\alpha}$.

---

(4) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389.

(5) The triethylsilyl (TES) enol ether exhibited greater stability than the corresponding trimethylsilyl (TMS) enol ether in the subsequent steps.

(6) Satisfactory spectral data (IR, ^{1}H and ^{13}C NMR, mass spectra) and elemental analyses were obtained for all new compounds.

(7) See ref 4 for a detailed procedure.

(8) The initial 1,4-adduct is a highly sensitive enol ether–allyl alcohol system, which should be rapidly hydrolyzed to the corresponding β-hydroxycyclopentanone in order to prevent elimination of the hydroxyl group.

(9) Newton, R. F.; Reynolds, D. P. *Tetrahedron Lett.* **1979**, 3981.

(10) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.

(11) Our synthetic prostaglandins were spectroscopically (IR, 360-MHz ^{1}H NMR, and ^{13}C NMR spectra) compared to authentic samples kindly supplied by Dr. D. R. Morton of Upjohn.

(12) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100.

(13) Similar results have been reported by Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755.

(14) For a review, see: Wenkert, E. *Acc. Chem. Res.* **1980** *13*, 27.

(15) Stereochemical assignments are based on 360-MHz ^{1}H NMR data of pure samples of each isomer. Also, their chemical structures have been unequivocally confirmed by independent conversion of each isomer into lactone **10**.

(16) For a detailed procedure, see: Reissig, H.-U.; Hirsch, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 813.

(17) Brown, H. C.; Dickason, W. C. *J. Am. Chem. Soc.* **1970**, *92*, 709.

(18) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373.

(19) Corey, E. J.; Weinshenker, N. M.; Schaff, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(20) The Wittig reaction was performed according to the procedure reported by Newton, R. F.; Reynolds, D. P.; Webb, C. F.; Young, S. N. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2789.

**Joseph P. Marino,* Roberto Fernández de la Pradilla
Edgardo Laborde**

*Department of Chemistry
The University of Michigan
Ann Arbor, Michigan 48109*

Received July 5, 1984

Direct Formation of Organocopper Compounds by Oxidative Addition of Zerovalent Copper to Organic Halides

Summary: Mixing a solution of CuI·P(Et)$_3$ with a stoichiometric amount of lithium naphthalide in THF affords a zerovalent copper species that is sufficiently reactive to add to organic halides to give the corresponding organocopper compounds.

Sir: Reports over the past several years have demonstrated the very versatile utility of organocopper compounds in synthesis.[1,2] The vast majority of these reports have

Scheme I

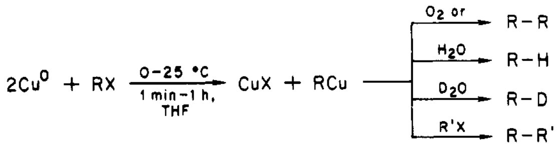


Table I. Homocoupling

$2RX + Cu^0$	yield of R-R, %	misc.	temp, °C	solvent
allyl bromide	99[a]		25	THF
C_6F_5I	91[a]	CuCl[b]	101	dioxane
$C_6H_5CH_2Br$	95[a]		25	THF
o-$NO_2C_6H_4I$	87[c]	$CuCl{\cdot}S(CH_3)2$[d]	65	THF
o-CNC_6H_4Br	76[c]	O_2[e]	25	THF
n-heptyl iodide	83[a]		25	THF/DMF
PhI	66[a]		85	glyme
PhC≡CBr	30[c]	O_2[e]	25	glyme

[a] GC yield. [b] Best results were obtained for this coupling by reducing CuCl powder in a solution of lithium naphthalide. [c] Isolated yield. [d] Reducing the sulfide complex gave better results than the phosphine complex. [e] After production of RCu, coupling was induced by injecting 100 mL of O_2 into the reaction vessel.

Table II. Stable Organocopper Intermediates

$RX + Cu^0$	→	yield of R-H, %	temp, °C	time	solvent
PhI	H_2O	98[a]	25	10 min	THF
o-$NO_2C_6H_4I$	H_2O	60[a]	0	1 min	THF/DMF
o-CNC_6H_4Br	H_2O	89[b]	0	1 h	THF
PhC≡CBr	H_2O	42[a]	25	18 h	glyme
C_6F_5I	H_2O	90[a]	25	1 min	THF
PhCH=CHBr	H_2O	66[b]	25	10 min	glyme
C_6F_5I	D_2O	90[a]	25	1 h	THF
PhCH=CHBr	D_2O	37[b]	25	20 h	THF

[a] GC yield. [b] Isolated yield.

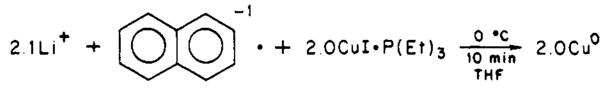
Table III. Cross-Coupling Reactions

RCu	R'X	R-R'	yield,[a] %
C_6F_5Cu	Ar(CO)Cl	C_6F_5(CO)Ar	25[a]
PhCu	Ar(CO)Cl	Ph(CO)Ar	70[b]
o-CNC_6H_4Cu	Ar(CO)Cl	*o*-CNC_6H_4(CO)Ar	95[a]
PhCu	CH_2=$CHCH_2Br$	$PhCH_2CH$=CH_2	36[b]
o-CNC_6H_4Cu	CH_3(CO)Cl	*o*-$CNC_6H_4(CO)CH_3$	46[a]
o-CNC_6H_4Cu	$C_6H_5CH_2Br$	*o*-$CNC_6H_4CH_2C_6H_5$	51[a]
PhCu	$ArCH_2Br$	$PhCH_2Ar$	84[b]
$PhCH_2Br$	CH_2=$CHCH_2Br$	$PhCH_2CH_2CH$=CH_2	50[b]
$CH_3(CH_2)_5CH_2I$	CH_2=$CHCH_2Br$	1-decene	45[b]

[a] Isolated yield. [b] GC yield.

utilized organocopper reagents prepared from organolithium[3] or Grignard[4] precursors along with the appropriate copper(I) salt. These two basic approaches greatly limit the functionality that can be incorporated in the organocopper reagents.[5] While a few other methods of preparing organocopper compounds have been reported, they are not of a general nature.[6-9]

We would like to report a new general approach for the preparation of organocopper reagents. The procedure involves the direct oxidative addition of highly reactive zerovalent copper to organic halides. Significantly, the organic halides can contain a wide variety of functional groups. The highly reactive zerovalent copper is prepared by the reduction of a copper(I) phosphine[10] complex with lithium naphthalide under an argon atmosphere.[11] This copper is much more reactive than the copper metal we reported previously.[16] The key to the metal's high reactivity is the fast, ambient temperature reduction made possible by using the soluble copper(I) phosphine complex and preformed lithium naphthalide. The resulting zerovalent copper will oxidatively add to alkyl, aryl, and vinyl halides under very mild conditions. This is the first report of such reactions under such mild conditions. While the exact nature of the resulting organocopper species is yet to be determined, the chemistry it displays provides convincing support for an organocopper(I) compound. A general scheme of some of the reactions observed is shown in Scheme I.



Homocoupling of organic halides is readily accomplished by using this copper. Moreover, the conditions employed are very mild compared to the Ullman synthesis of biaryls.[13] Table I presents a summary of some of these homocoupling reactions. Upon addition to the zerovalent copper, most alkyl halides self-couple in less than 1 min. Very little reduced product (toluene, heptane, propene) is formed. It is interesting to note that for compounds containing β hydrogens, such as *n*-heptyl iodide, the coupling is unknown for the Ullman synthesis and traditional alkylcuprates eliminate to give alkenes under these conditions.[14] At 25 °C, for aryl and alkynyl halides, the reaction tends to stop at the formation of the organocopper complex. Moderate heating usually forces the reaction to proceed to the coupled product. If excessive heating is required, as in the case for *o*-CNC_6H_4Br and PhC≡CBr, homocoupling can be achieved by introducing molecular oxygen into the reaction vessel.[15]

---

(1) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.

(2) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1.

(3) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.

(4) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.

(5) Ketones, esters, nitriles, and even alcohols can be present in the substrate molecule; see ref 1 and 2.

(6) Fanta, P. E. *Synthesis* 1974, 9. Fanta, P. E. *Chem. Rev 64*, 613.

(7) Cairncross, A.; Roland, J.; Henderson, R.; Sheppard, W. *J. Am. Chem. Soc.* **1970**, *92*, 3187.

(8) Bolth, F.; Whaley, W.; Starkey, E. *J. Am. Chem. Soc.* **1943**, *65*, 1456.

(9) McLoughlin, V.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921.

(10) Preparation of $CuI{\cdot}P(Et)_3$: Kauffman, G.; Teter, L. *Inorg. Synth.* **1963**, *7*, 9.

(11) Typically Li^0 (21 mmol) and naphthalene (22 mmol) in 20 mL of glyme or THF are stirred for 2 h under argon. Then a solution of $CuI{\cdot}P(Et)_3$ (20 mmol) in 5 mL of glyme or THF is syringed into the lithium naphthalide and stirred for 10 min at 0 °C. For alkyl halide homocoupling, 10 mmol of the alkyl halide is syringed into 20 mmol of the zerovalent copper which as been precooled to 0 °C due to the exothermic nature of these reactions. For the cross-coupled reactions, 5 mmol of each alkyl halide is mixed in a small amount of solvent, and the resulting mixture is syringed into the copper. The reactions are complete between 1 and 10 min. Formation of the stable aryl, alkenyl, and alkynyl copper compounds is accomplished by mixing 10 mmol of the organic halide with 20 mmol of the precooled activated copper. Maximum yield is usually achieved between 10 and 60 min. To cross-couple, add the second reagent and stir for 1 h at 0 °C, an additional hour at room temperature, and a final hour at reflux. To homocouple the arylcopper compound, heat the reaction vessel to reflux for several hours or bubble oxygen into the reaction for 1 h.

(12) All compounds synthesized were known compounds previously reported in the literature and most are commercially available. When an authentic sample was procurable the reactions were run with an internal standard and quantitation was performed by gas chromatography analysis. Other yields were isolated yields. Identification of the compounds was verified through standard workup procedures and a comparison of the physical and spectral properties of the isolated compound with authentic samples or with the data reported in the literature.

(13) Goshave, M.; Otroshchenko, O. S.; Sadykov, A. S. *Russ. Chem. Rev., Engl. Tranl.* **1972**, *41*, 1046.

(14) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

(15) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1972**, *42*, 205.

Nearly all alkynyl, alkenyl, and aryl halides studied will form stable organocopper compounds at 25 °C or lower as evidenced by the fact that quenching the reactions with water produces the reduced products "R–H" in moderate to excellent yields. Earlier workers in this laboratory isolated and characterized C_6F_5Cu produced from the reaction of C_6F_5I with a much less reactive Cu^0.[16] In addition, quenching C_6F_5Cu and PhCH=CHCu with D_2O produces the expected deuterated product in moderate to good yield. Table II summarizes some of the stable organocopper species produced.

Cross-coupled products can also be formed with the stable organocopper species. Table III summarizes some of the cross-coupling reactions which we have attempted to date. Reaction of the arylcopper compounds with benzoyl chloride produces benzophenones in high yield. Reaction of PhCu with reactive halides such as allyl or benzyl bromide yields the desired product in only low to moderate yield. The major products in these reactions are the homocoupled bibenzyl and 1,5-hexadiene. If two alkyl halides are mixed in equal molar amounts and then allowed to react with copper, a mixture of all three possible products is formed in approxiamately the statistically expected amounts.

In summary, a highly reactive zerovalent copper has been produced. The copper undergoes rapid oxidative addition under very mild conditions into alkyl, aryl, and vinyl halides. Significantly, the organic halides can contain a variety of functional groups. These organocopper species formed undergo several reactions described for traditional organocuperates. Accordingly, we feel this approach will significantly improve the general utility of organocopper intermediates.

Acknowledgment. We gratefully acknowledge support of this work by the Division of Chemical Sciences, Department of Energy (Contract No. De-AC02-80ER10603), and the U.S. Army Research Office.

---

[16] Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445.

Greg W. Ebert, Reuben D. Rieke*
Department of Chemistry
University of Nebraska-Lincoln
Lincoln, Nebraska 68588-0304

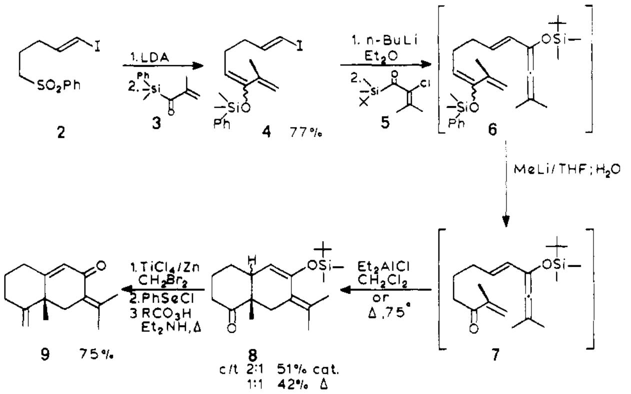
Received October 29, 1984

Silyl Ketone Chemistry. Preparation of Eremophilane and Eudesmane Sesquiterpenes by Vinylallene Cycloaddition[1]

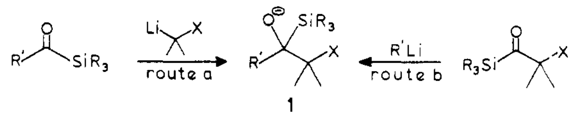
Summary: The Diels–Alder cyclization of enone siloxyvinylallenes leading to dehydrofukinone and selina-4(14),7(11)-dien-8-one are described. Several silyl ketone (acylsilane) reactions were used to prepare key enol silyl ether intermediates.

Sir: A wide range of enol ethers can be prepared from β-X-substituted-α-silylalkoxides 1 by a sequence involving C to O silyl migration with concomitant expulsion of X.[1b,c,2]

Scheme I



The precursor 1 is available by several routes, two of which are shown in eq 1. The mildness of the reaction conditions



(1)

and flexibility of the method make it attractive for the preparation of polyfunctional molecules. We report here several applications of this chemistry to the efficient synthesis of siloxyvinylallene enones, as well as studies of their Diels–Alder cyclization[3] to eremophilane and eudesmane sesquiterpenes.

The key steps of the synthesis are outlined in Scheme I. The α-lithio sulfone prepared by deprotonation of sulfonyl vinyl iodide (LDA, THF, −78 °C, 20 min) 2 reacted smoothly with 2-propenyl phenyldimethylsilyl ketone (**3**)[4] (eq 1, route a) to give siloxy diene **4** (1:3 *E*/*Z* mixture). This material, which could be purified by short column chromatography, was subjected to metal–halogen exchange (n-BuLi, Et_2O, −78 °C, 20 min), and the vinyllithium reagent so formed was treated with α-chloro silyl enone **5**,[1c] giving directly the vinylallene **6** (eq 1, route b). Cleavage of the phenyldimethylsilyl enol ether in the presence of TBDMS proceeded smoothly (MeLi, THF, −78 °C to 0 °C) and led after enolate protonation to the key intermediate **7**. Cycloaddition was best accomplished by Lewis acid catalysis (Et_2AlCl, 1.1 equiv; CH_2Cl_2, −78 °C to 0 °C) but could also be carried out thermally. Neither **6** nor **7** was purified (although characterized by NMR spectroscopy) so the yields of **8** quoted are over the three steps **4** to **8**. The cycloaddition gave mixtures of *cis*- and *trans*-decalin structures, with cis being favored by a 2:1 margin in the Et_2AlCl-catalyzed reaction.[6] The synthesis

---

[1] For earlier papers in this series, see: (a) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423. (b) Reich, H. J.; Rusek, J. J.; Olson, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 2225. (c) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949. Reich, H. J.; Kelly, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 1119.

[2] Brook, A. G.; Fieldhouse, S. A. *J. Organomet. Chem.* **1967**, *10*, 235. Brook, A. G.; Limburg, W. W.; MacRae, D. M.; Fieldhouse, S. A. *J. Am. Chem. Soc.* **1967**, *89*, 704. Kuwajima, I.; Atsumi, K.; Tanaka, T.; Inoue, T. *Chem. Lett.* **1979**, 1239. Kuwajima, I.; Kato, M. *Tetrahedron Lett.* **1980**, *21*, 623.

[3] Diels–Alder reactions of vinylallenes have not been studied extensively. Intermolecular: Jones, E. R. H.; Lee, H. H.; Whiting, M. C. *J. Chem. Soc.* **1960**, 341. Fedorova, A. V.; Petrov, A. A. *Zh. Obsch. Khim.* **1962**, *32*, 3537. Bertrand, M.; Grimaldi, J.; Waegell, B. *Bull. Soc. Chim. Fr.* **1971**, 962. Heldeweg, R. F.; Hogeveen, H. *J. Org. Chem.* **1978**, *43*, 1916. Intramolecular: Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682. Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370.

[4] This ketone was prepared by addition of (phenyldimethylsilyl)lithium (Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520) to methacrolein (THF/Et_2O, −78 °C, 71% yield) followed by Swern oxidation[5] (Me_2SO, $(COCl)_2$, NEt_3, −50 °C to 25 °C, 83% yield).

[5] Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

[6] We have been able to locate one nonallenic Diels–Alder cyclization similar to the transformation of 7 to 8 i.e., introduction of an angular methyl group (unpublished result of D. F. Taber and B. P. Gunn cited in E. Ciganek, *Org. React.* (*N.Y.*) **1984**, *32*, 1 (entry 27, Table 3a)). This system gave a 42/21 ratio of cis/trans ring-fusion products.

0022-3263/84/1949-5282$01.50/0 © 1984 American Chemical Society