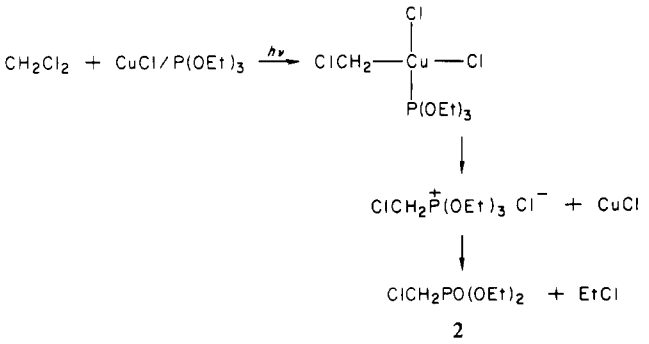
Scheme III



acrylate may also be explained reasonably by a similar two electron oxidative addition–reductive elimination pathway (Scheme III). **2** was not obtained without assistance of photoirradiation or in a photochemical reaction without CuCl catalyst. The reactions of Scheme II and III further suggest that pathway a and not b of Scheme I is involved in copper(I)-catalyzed photoaddition of alkyl halides to olefins.

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Registry No. $CH_3(CH_2)_3Br$, 109-65-9; c-$C_6H_{11}Br$, 108-85-0; $(C_6H_5)_3CBr$, 507-19-7; $Br(CH_2)_4Br$, 110-52-1; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_2COOEt$, 539-74-2; $CH_3(CH_2)_3Cl$, 109-69-3; CH_2=CHCN, 107-13-1; CH_2=CHCOOEt, 140-88-5; CH_2=CHCOMe, 78-94-4; CH_2=C(Me)CN, 126-98-7; CH_2=C(Me)COOEt, 97-63-2; CH_2=C(COOEt)CH_2COOEt, 2409-52-1; *cis*-CH(COOEt)=CH(COOEt), 141-05-9; CuCl, 7758-89-6; CuBr, 7787-70-4; $(n\text{-}Bu)_3P$, 998-40-3; $CH_3(CH_2)_4CHBrCN$, 38799-37-0; $CH_3(CH_2)_4CHBrCOOEt$, 5333-88-0; c-$C_6H_{11}CH_2CHBrCN$, 87319-36-6; c-$C_6H_{11}CH_2CHBrCOOEt$, 77100-90-4; $(CH_3)_3CCH_2CHBrCN$, 87319-37-7; $Br(CH_2)_5CHBrCN$, 87319-38-8; $Br(CH_2)_4CHBrCN$, 87319-39-9; $Br(CH_2)_4CHBrCOOEt$, 29512-97-8; $Br(CH_2)_4CHBrCOMe$, 87319-40-2; $Br(CH_2)_4C(Me)BrCN$, 87319-41-3; $Br(CH_2)_4C(Me)BrCOOEt$, 87319-42-4; $Br(CH_2)_4C(COOEt)BrCH_2COOEt$, 87319-43-5; $Br(CH_2)_3CH(COOEt)CHBrCOOEt$, 87319-44-6; $Br(CH_2)_3CHBrCN$, 87319-45-7; $EtOOC(CH_2)3CHBrCN$, 87319-46-8.

Enantioselective Cyclopropane Synthesis Using the Chiral Carbene Complexes ($S_{Fe}S_C$)- and ($R_{Fe}S_C$)-(C_5H_5)(CO)(Ph_2R^*P)Fe=$CHCH_3^+$ (R^* = (*S*)-2-Methylbutyl). Role of Metal vs. Ligand Chirality in the Optical Induction

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Transfer of the carbene ligand from optically active transition-metal carbene complexes to alkenes represents a potentially useful and general method for the enantioselective synthesis of cyclopropanes;[1-7] however, few practical systems have been reported. Recently, synthetic utility has been demonstrated for preparation of cyclopropanes from the reactions of alkenes with electrophilic, cationic carbene complexes of the general structure $Cp(CO)_2Fe$=CRR'^+ (R = R′ = H;[8] R = H, R′ = aryl;[9] R = H, R′ = CH_3;[10-12] R = R′ = CH_3[13]). We report here the in situ

Scheme I

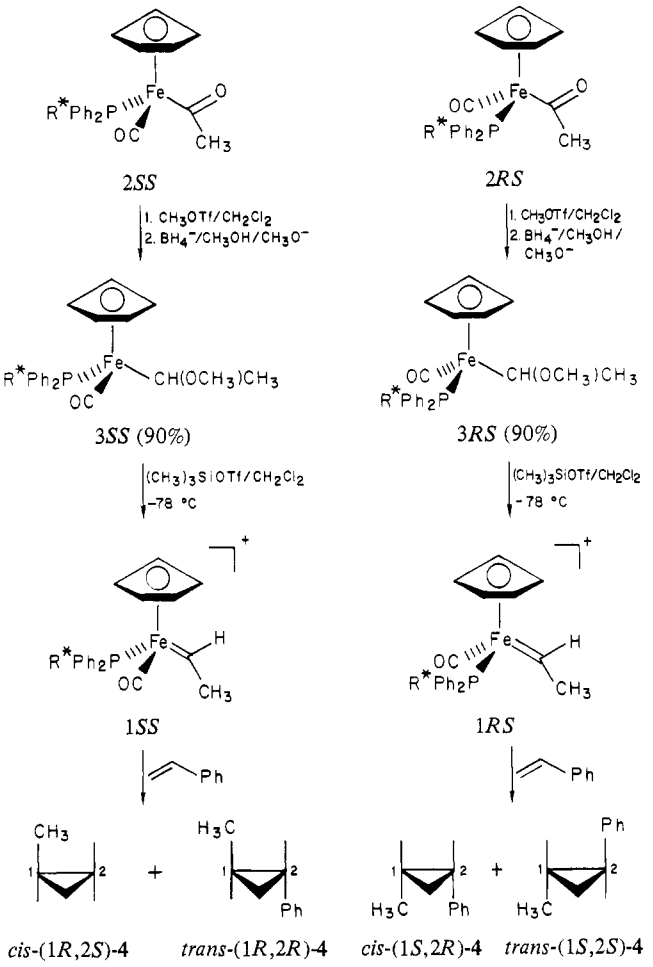

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Table I. Optical Rotations, % ee's, and Optical Yields of Product Cyclopropanes, *cis*- and *trans*-4

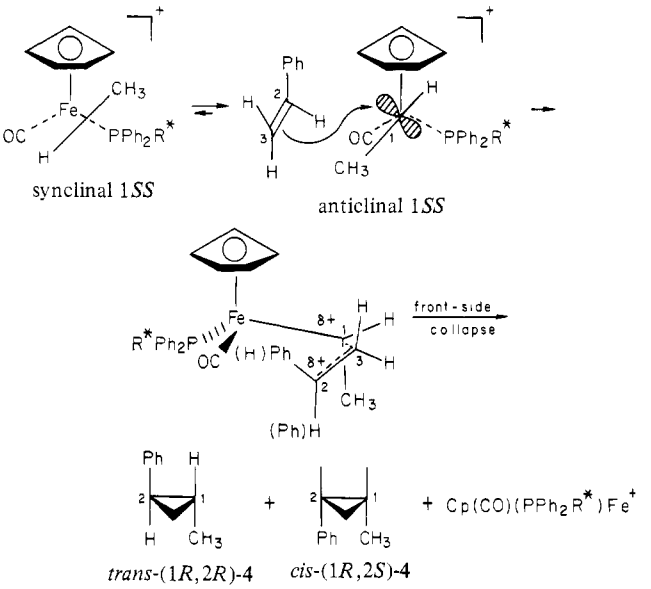
acyl precursor 2*SS*:2*RS*	*trans*-4:*cis*-4 ratio	major enantiomers of 4 produced	optical rotation[a] $[\alpha]^{25}_D$, deg	concn[a,b]	ee,[c] %	optical yield, %
99:1	3.5:1	*trans*-1*R*,2*R*	−101 ± 4	1.92, 2.81, 1.45	88 ± 3	90 ± 3
		cis-1*R*,2*S*	−54 ± 2	0.27, 0.59	84 ± 3	86 ± 3
4:96	4.0:1	*trans*-1*S*,2*S*	+96 ± 2	6.05, 7.78, 6.42	83 ± 2	90 ± 2
		cis-1*S*,2*R*	+49 ± 2	0.98, 0.56	77 ± 3	84 ± 3

[a] Concentrations in g/100 mL of GLC-purified cyclopropanes used for $[\alpha]^{25}_D$ determinations. [b] Solvents $CHCl_3$ and CH_3CH_2OH were found to give the same results within experimental error. [c] Based on rotations quoted in ref 3d and 23. Optical rotations of $[\alpha]^{25}_D$ +96° (CH_3CH_2OH)[22] and $[\alpha]^{26}_D$ −114.9° ($CHCl_3$)[3d] have been reported for (1*S*,2*S*)-4 and (1*R*,2*R*)-4, respectively. The higher value was used to calculate ee's.

generation of two diastereomeric ethylidene complexes, ($S_{Fe}S_C$)- and ($R_{Fe}S_C$)-Cp(CO)(PPh_2R^*)Fe=$CHCH_3^+$, 1*SS* and 1*RS* (R* = (*S*)-2-methylbutyl), differing only in the configuration at iron,[14] and the efficient transfer of ethylidene from each of these complexes to styrene to give *cis*- and *trans*-1-methyl-2-phenylcyclopropanes with high enantiomeric excesses. These observations show that chiral carbene complexes of the type Cp(CO)(L)Fe=CHR^+ should have general utility for enantioselective cyclopropane synthesis.

The sequence of reactions carried out is summarized in Scheme I. Chromatographic separation (silica gel) of the diastereomeric acyl complexes ($S_{Fe}S_C$)- and ($R_{Fe}S_C$)-Cp(CO)(Ph_2R^*P)$FeCOCH_3$ gives a solid diastereomer, 2*SS* (purified to 99:1, 2*SS*/2*RS*), and an oily diastereomer, 2*RS* (96:4, 2*RS*/2*SS*).[15] CD spectra of 2*SS* and 2*RS* unambiguously established the configuration at iron.[16-18] The acyls 2*SS* and 2*RS* were converted to the α-ethers 3*SS* and 3*RS*[19] by the alkylation–reduction procedure shown and previously described.[10b] Treatment of 3*SS* or 3*RS* with trimethylsilyl triflate in the presence of styrene results in in situ generation[20] of 1*SS* or 1*RS* followed by transfer of ethylidene to give 3.5 ± 0.2:1 and 4.0 ± 0.2:1 ratios of *trans*-to *cis*-1-methyl-2-phenylcyclopropanes, **4** (75% yield).[21] Separation by GLC[10b] gave pure (>99%) samples of *cis*-**4** and *trans*-**4** whose absolute configurations, optical rotations, and ee's are summarized in Table I.

Correcting for diastereomeric impurities, the optical yields of *cis*-(1*R*,2*S*)-**4** and *trans*-(1*R*,2*R*)-**4** from 1*SS* are ca. 86 and 90%, respectively. Similary, pure 1*RS* yields *cis*-(1*S*,2*R*)-**4** and *trans*-(1*S*,2*S*)-**4**, in ca. 84 and 90% ee. For 1*SS* these results are interpreted on the basis of the following model:



The nucleophile, styrene, attacks anticlinal 1*SS* over CO at the si face of the ethylidene with initial interaction between C_1 and C_3. The developing electrophilic center at C_2 then ultimately collapses in a front-side manner (either concertedly or via a metallacyclic intermediate[10b]) to give the *cis*- and *trans*-cyclopropane enantiomers observed, depending on whether styrene adds with its si or re face.

There are several assumptions implicit in this proposed mechanism, but all have precedent. The structures of Cp(NO)(PPh_3)Re=CHR^+ (R = alkyl, aryl)[24] and related calculations[24a,25] suggest that, in complexes of the type 1*SS*, the carbene plane will be aligned with the Fe–CO bond giving anticlinal and synclinal isomers with anticlinal 1*SS* favored on steric grounds.[24] Styrene attack on the si face or anticlinal 1*SS* is suggested by the steric shielding of the re face in 1*SS* and the observation by Gladysz that nucleophiles attack anticlinal (*S*)-Cp(NO)(PPh_3)-Re=CHR^+ stereospecifically on the si face.[24] Furthermore, addition of hydride to the carbene carbon of $Cp(CO)_2MoC$-

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(14) Based on the priority sequence C_5H_5 > PPh_2R^* > CO > $COCH_3$/$CH(OCH_3)CH_3$/$CHCH_3$.[2]

(15) Spectral data for 2*SS* and 2*RR* contained in the supplementary material.

(16) The CD spectra of 2*SS* and 2*RS* (see supplementary material) were correlated with CD spectra of similar acyl complexes of known configuration, Cp(CO)(PPh_3)$FeCOCH_3$[17] and Cp(CO)($PPh_2NHCH(CH)(Ph)FeCOCH_3$.[18]

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(19) Spectral data for 3*SS* and 3*RS* contained in the supplementary material. Although two diastereomers for each of 3*SS* and 3*RS* can be formed, only one is detected by ^1H NMR. The configurations generated at C_1 are unknown.

(20) ^1H NMR spectra confirm formation of carbene complexes 1*SS* and 1*RS* when 3*SS* and 3*RS* react with 2 equiv of trimethylsilyl triflate in CD_2Cl_2 at −78 °C. In each case low-field resonances of H_1(δ 17.27 for 1*SS*, δ 17.42 for 1*RS*) diagnostic of cationic ethylidene species[10,12] proved the presence of 1*SS* and 1*RS*.

(21) In a typical procedure, trimethylsilyl triflate (1.35 mmol) is added to a CH_2Cl_2 solution (−78 °C) containing either 3*SS* or 3*RS* (1.3 mmol), styrene (10 mmol), and triethylamine (0.05 mmol) followed by slow warming to 25 °C and standard workup.[10b]

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$(Ph)N(CH_3)C(Ph)N(CH_3)^+$ occurs from the Cp side.[26] The initial attack of C_1 at C_3 is strongly supported by earlier work on reactions of electrophilic carbene complexes.[9,10,27]

In the model presented, the assumption is made that the major reaction pathway proceeds via the anticlinal isomers of 1*SS* and 1*RS*. For the alkylidene complexes, $Cp(NO)(PPh_3)Re{=}CHR^+$ (R = CH_3, CH_2CH_3), the anticlinal isomer is favored with respect to the synclinal isomer by ca. 9:1.[24b,f] Taking into account the low rotational barrier around the iron–carbon bond,[10,28] there must be rapid equilibration between anticlinal and synclinal isomers of 1*SS* and 1*RS*, as shown above. Although the anticlinal isomer is likely favored, it is possible that transfer occurs via a minor, but more reactive, synclinal isomer. For example, a mechanism consistent with our results is styrene attack over CO on the synclinal isomers of 1*SS* and 1*RS* followed by *backside* displacement of $Cp(CO)(PPh_2R^*)Fe^+$ by the developing electrophilic center at C_2.[10b,c] A second, perhaps more likely consequence of the presence of minor amounts of synclinal 1*SS* and 1*RS* is that the minor enantiomers arise via these isomers.

Compared to the high ee's in ethylidene transfer from 1*SS* and 1*RS* to styrene, methylene transfer from $Cp(CO)(PPh_3)FeCH_2X$ derivatives to *trans*-β-methylstyrene occurs with substantially less stereoselectively, only 10–35%.[5,6] The difference is likely due to the fact that in 1*SS* and 1*RS* the carbene carbon, C_1, is prochiral whereas in $Cp(CO)(PPh_3)FeCH_2X$ it is not. In analogy with nucleophilic attack on $Cp(NO)(PPh_3)Re{=}CHC_6H_5^+$,[24] high asymmetric induction in the present systems results from selective attack of styrene on one face of the prochiral ethylidene ligand in 1*SS* and 1*RS*, controlled by a preferred orientation of the carbene ligand and large steric differences in the ancillary ligands.[29]

In enantioselective catalysis, optically active metal ligands, usually phosphines, carry the chiral information.[30] During catalysis the metal atom itself can become a chiral center, and the role of the metal chirality in enantioselective transformations has been discussed.[30–33] The present cyclopropanation of styrene is of interest in this respect. 1*SS* and 1*RS* contain the same optically active phosphine ligand yet have opposite metal configurations. The fact that 1*SS* and 1*RS* give cyclopropanes of *opposite* configurations in almost identical optical purities indicates that the chirality at the *iron* is primarily responsible for asymmetric induction and that the phosphine chirality plays little or no role, demonstrating the potential for control by the metal configuration in enantioselective catalysis.

The present results show that chiral carbene complexes of the type $Cp(CO)(PR_3)Fe{=}CHR^+$ will be generally useful for asymmetric syntheses of cyclopropanes. The features critical to high enantioselectivity and further applications of these reactions are being investigated.

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Supplementary Material Available: CD spectra of $(S_{Fe}S_C)$- and $(R_{Fe}S_C)$-$Cp(CO)(PPh_2R^*)FeCOCH_3$, R* = (*S*)-2-methylbutyl, and spectral data (^1H NMR, IR, optical rotations) for 2*SS*, 2*RS*, 3*SS*, and 3*RS* (3 pages). Ordering information is given on any current masthead page.

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Application of the Furan–Carbonyl Photocycloaddition Reaction to the Synthesis of the Bis(tetrahydrofuran) Moiety of Asteltoxin

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Asteltoxin **1**, isolated from toxic maize cultures of *Aspergillus stellatus* by Vleggaar and co-workers,[2] is a potent inhibitor of *E. coli* BF_1-ATPase activity and serves as a valuable fluorescent probe of mitochondrial F_1- and bacterial BF_1-ATPase.[3] Evidence suggests that the bis(tetrahydrofuran) moiety is responsible for the inhibition and binding properties of asteltoxin.[3] Analysis of this hindered ring system (Scheme I) revealed that the open (hydrolyzed) form of asteltoxin, **3**, would be obtained from a threo-aldol condensation of **4** and **5** or their equivalents in the indicated manner. We have recently reported a method for stereoselective threo-aldol formation, which employs the Paterno–Büchi photocycloaddition of a furan and an aldehyde.[4,5] The application of this methodology to the synthesis of **2** is reported herein.

The functionalized photoaldol[4] **9** was conveniently prepared in multigram quantities by a two-step sequence (Scheme II).[6] Irradiation of 3,4-dimethylfuran[7] (12 g) and β-(benzyloxy)-propanal (8.9 g) in benzene (200 mL, 0.27 M) for 6 h with a 450 W Hanovia lamp equipped with a Vycor filter afforded a single exo-photoadduct **8** that was most efficiently treated directly with MCPBA to provide **9** (10.7 g, 45% from **7**). Hydrolysis afforded the aldehyde **10**, which exists as the monocyclic hemiacetal. *It should be noted that this three-step reaction sequence provides the threo-aldol* **10** *with complete control of stereochemistry at the quaternary carbon.*

Protection of the more reactive[8] aldehyde with dimethylhydrazine produced the hydrazone **11**. Introduction of the β-ethyl side chain could be achieved with complete stereochemical control by chelation-controlled[12c] addition of excess EtMgBr to the latent α-hydroxy aldehyde **11**.[9] Internal protection of the hydrolysis product as the acetonide afforded **12**. Deprotection of the benzyl ether, selenenylation,[10] and selenoxide elimination gave **15** in high yield.

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(6) All compounds reported gave ^{13}C NMR (22.5 MHz), ^1H NMR (500 MHz), FT-IR, and mass spectra (low resolution) in accord with the structure given. Exact mass measurements (CI) were obtained for compounds **2**, **9**, **11**, **12**, **15**, and **23**. Spectral data are available in the supplementary material.
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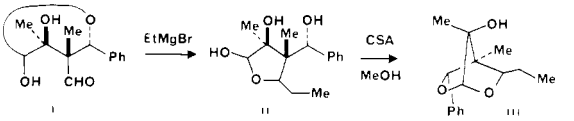
(8) Treatment of the related compound i with 3 equiv of EtMgBr provided a single product ii resulting from addition to the exposed aldehyde, which afforded the bridged acetal iii after acid-catalyzed cyclization in methanol.



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