of Fe^{4+} to Fe^{3+} were observed at 564 nm[11] on a time scale of seconds. The time course of this slow reaction (Figure 2) is dependent on the concentration of a_5Ru^{3+}(His-60)CCP(Fe^{4+}) present in the samples. At ≥10 μM protein, the traces are clearly biphasic and the faster, dominant phase yields a pseudo-first-order rate constant which is dependent on protein concentration in the range 10–40 μM, and is assumed to arise from *intermolecular* reduction of the Fe^{4+} center:

$$a_5Ru^{2+}(His\text{-}60)CCP(Fe^{4+}) + a_5Ru^{3+}(His\text{-}60)CCP(Fe^{4+}) \xrightarrow{k_2} a_5Ru^{3+}(His\text{-}60)CCP(Fe^{4+}) + a_5Ru^{3+}(His\text{-}60)CCP(Fe^{3+}) \quad (1)$$

where $k_2 = 1.2 \times 10^6\ M^{-1}\ s^{-1}$. This value is comparable to that obtained for the reduction of CCP(Fe^{4+}) by free a_5Ru^{2+}py ($k_2 = 9.5 \times 10^6\ M^{-1}\ s^{-1}$),[12] indicating that the covalently attached Ru center is highly exposed, as is evident from Figure 1.

The slower phase, which essentially disappears at 40 μM protein (Figure 2c), yields a first-order rate constant, $k_1 = 3.2 \pm 1.2\ s^{-1}$, which is independent of protein concentration. This process is assigned to *intramolecular* reduction of the Fe^{4+} center by the surface-bound Ru^{2+}:

$$a_5Ru^{2+}(His\text{-}60)CCP(Fe^{4+}) \xrightarrow{k_1} a_5Ru^{3+}(His\text{-}60)CCP(Fe^{3+}) \quad (2)$$

The rate of intramolecular reduction of the Fe^{4+} is surprisingly slow considering the large driving force for this reaction ($\Delta E^\circ \sim 1$ V)[13] and the 21.8-Å separation from His-60 to the heme (Figure 1). At a lower driving force ($\Delta E^\circ \sim 0.8$ V), rates of 85–100 s^{-1} were observed for electron transfer from the Zn protoporphyrin triplet state to Ru^{3+} in three different a_5Ru^{3+} derivatives of Zn-substituted myoglobin with 19–22-Å separation between the redox centers.[14] Similarly, rapid (10^2–$10^4\ s^{-1}$) intracomplex electron transfer has been observed in the electrostatically stabilized complexes[15] between the natural partners yeast cytochrome *c* (cyt *c*) and CCP(Fe^{4+})[16] or Zn-substituted CCP.[17] However, these rates are highly sensitive to the source (yeast, horse, etc.) of cyt *c*, as well as the ionic strength, suggesting that changes at the protein–protein interface play a dominant role in the control of the intracomplex rates.[10,16-18]

No protein–protein interface is traversed in the slow intramolecular electron transfer in eq 2. This raises the possibility that the reorganization energy associated with the conversion of 6-coordinate low-spin Fe^{4+} to 5-coordinate high-spin Fe^{3+},[19] which involves dissociation of the Fe^{4+}=O bond in the former,[1] may be quite large. It is also possible that there is no efficient electron-transfer pathway from His-60 to the heme. In fact, addition of cyt *c*(Fe^{3+}) at low ionic strength does not affect the reduction of the a_5Ru^{3+} center, indicating that cyt *c* does not interact with CCP in this region,[20] which obviates the need for electron transfer between His-60 and the heme. Furthermore, the intramolecular electron transfer rate does not change on cyt *c* binding, which eliminates the possibility of cyt *c* acting as a gating switch to allow facile electron transfer from nonspecific surface regions.

To examine the reasons for this slow electron-transfer rate, other derivatives of CCP are being prepared.[21] We also plan to prepare a_5Ru^{3+} derivatives of CCP(Zn) to compare their electron-transfer reactivities with those reported for the myoglobin derivatives.[14]

Acknowledgment. We thank Professors Alison Butler (Santa Barbara) and Harry Gray (Caltech) for their assistance in our first attempts to ruthenate CCP. This work was supported by NSERC (Canada) Grant A1530 (to A.M.E.), NSF Grant DMB-8716316 (to T.L.P.), and NIH Grant DK15057 (to G.T.).

(11) $\Delta\epsilon$ is ~8 $mM^{-1}\ cm^{-1}$ at this wavelength (Yonetani, T. *The Enzymes Vol 18*; Boyer, P. D., Ed.; Academic Press: New York, 1976; pp 345–361), which we found to be a maximum in the CCP(Fe^{4+}) – CCP(Fe^{3+}) difference spectrum. There is no evidence to suggest that the rate of reduction of Ru^{3+} attached to CCP(Fe^{4+}) should be any different from that attached to CCP(Fe^{3+}). Thus, DRFH* reduction of the Fe^{4+} center on the slow time scale is not possible, and Fe^{3+} production must be due to electron transfer from Ru^{2+}.

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(14) Axup, A. W.; Albin, M.; Mayo, S. L.; Crutchley, R. J.; Gray, H. B. *J. Am. Chem. Soc.* **1988**, *110*, 435.

(15) The porphyrin-to-porphyrin separation in the noncovalent CCP–cyt *c* complex is not known, but a separation distance of ~16 Å was estimated from a computer graphics model of the complex (Poulos, T. L.; Kraut, J. *J. Biol. Chem.* **1980**, *255*, 10322. Poulos, T. L.; Finzel, B. C. *Pept. Protein Rev.* **1984**, *4*, 115).

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(18) Ho, P. S.; Sutoris, C.; Liang, N.; Margoliash, E.; Hoffman, B. M. *J. Am. Chem. Soc.* **1985**, *107*, 1070.

(19) Smulevich, G.; Mantini, A. R.; English, A. M.; Mauro, J. M. *Biochemistry* **1989**, *28*, 5058.

(20) This is in agreement with Brownian dynamics computer simulations of the association of cyt *c* and CCP which do not indicate a binding site for cyt *c* in the region of His-60 (Northrup, S. H.; Boles, J. O.; Reynolds, J. C. L. *Science* **1988**, *241*, 67).

(21) An investigation of the reorganization energy by a temperature-dependence study of the intramolecular electron transfer rate is extremely difficult for the His-60 derivative because the inter- and intramolecular processes occur on overlapping time scales at the lowest protein concentration required (1 μM) to obtain a reasonable signal-to-noise ratio.

Carbocupration of Cyclopropene. Asymmetric Synthesis of Quaternary Carbon Centers

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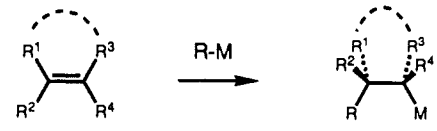
Carbometalation of a substituted olefin creates an organometallic species bearing two contiguous chiral centers (eq 1). If an effective method were available to make such a process asymmetric, then this reaction would acquire great utility as a method for the preparation of homochiral compounds.



(1)

We report that in the *cis*-carbocupration[1,2] of homochiral spirocyclic cyclopropenes **2** the asymmetric environment in the ketal moiety may be effectively transmitted through the spiro linkage to the rather distant olefinic portion of the molecule. Thus, the reaction generates highly synthetically useful[1] chiral copper reagents **3** and **4**, in which the cyclopropyl ring carbons are asymmetrically and differentially functionalized (Scheme I). Particularly notable is the regio- and stereoselective carbocupration of substituted cyclopropenes **2b,c**, which afforded cyclopropylcopper reagents **4b,c** bearing a chiral quaternary carbon center.[3]

The C_2-homochiral cyclopropene **2a** was prepared in 85% distilled yield by treatment of the ketal **1** with KNH_2 in liquid NH_3,[4] and the substituted derivatives **2b,c** were prepared by lithiation of **2a** with BuLi followed by alkylation under our previously reported conditions.[5]

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0002-7863/90/1512-7428$02.50/0

Scheme I

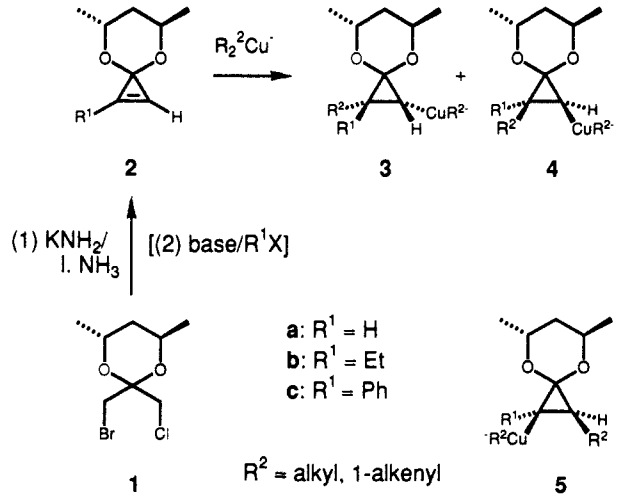

Table I. Stereoselective Carbocupration of **2**[a]

entry	2	R_2Cu^-	% yield (3 + 4)[b,c]	3:4[b,d]
1	**2a**	Me_2CuLi	77	72:28
2	**2a**	Bu_2CuLi	85	71:29
3	**2a**	$Bu_2CuMgBr$	90	65:35
4	**2a**	$Hex_2CuMgBr$	90	60:40
5	**2a**	*trans*-1-hexenyl-Cu(CN)(Th)Li_2[e]	84	96:4
6	**2b**	Me_2CuLi	89	4:96
7	**2b**	$Me_2CuMgBr$	92	10:90
8	**2c**	Me_2CuLi	65	0.9:99.1
9	**2c**	$Me_2CuMgBr$	78	8:92
11	**2c**	$Et_2CuMgBr$	90	3:97
11	**2c**	Bu_2CuLi	81	3:97

[a] The reactions were carried out as previously described (ref 1) at −70 °C in THF (entries 1–5) or in THF/DME (entries 6–11). The stereochemistry of the addition has been proven for the reactions in entries 4–7 and 10 (see the text and supplementary material), and others were assigned by analogy. [b] The yield and the **3**:**4** ratio have been determined for the cyclopropanone ketals (e.g., **10**) obtained after aqueous workup of the reaction mixture. [c] Isolated yield. [d] Determined by capillary GLC and ^{13}C NMR. [e] Th = 2-thienyl (ref 7).

Carbocupration of the chiral cyclopropenes **2** was carried out in THF at −70 °C as reported for the achiral compounds.[1] We have now found that, in addition to the Gilman reagents,[6] $R_2CuMgBr$-type reagents (from 2 equiv of RMgBr and CuBr·Me_2S) also undergo a smooth carbocupration reaction. The reactions of the parent compound **2a** with various cuprates generally proceeded with moderate stereoselectivity (Table I, entries 1–4), except for the reaction of a higher order vinylic cuprate reagent,[7] which proceeded with 96% diastereoselectivity (entry 5).[8]

The reaction of the 2-substituted cyclopropenes (**2b**,**c**) could potentially afford a mixture of 2,2-dialkyl (e.g., **3**) and 2,3-dialkyl products (e.g., **5**). In actuality, the regiochemical course of the addition reaction heavily favored the formation of the 2,2-dialkyl adduct. Thus, the (2,2):(2,3) ratio for the reaction of the 2-ethyl compound **2b** was >99:1 and, for the 2-phenyl derivative **2c**, 29:1–99:1. With respect to diastereoselectivity, we were pleased to find that the substituted compounds **2b**,**c** react much more selectively than **2a**, and surprisingly, *the sense of the addition is opposite to that observed for* **2a** (entries 6–11). Use of dimethoxyethane (DME) as a cosolvent has been found to slightly improve both the regio- and stereoselectivity of the carbometalation.

(6) Review: Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

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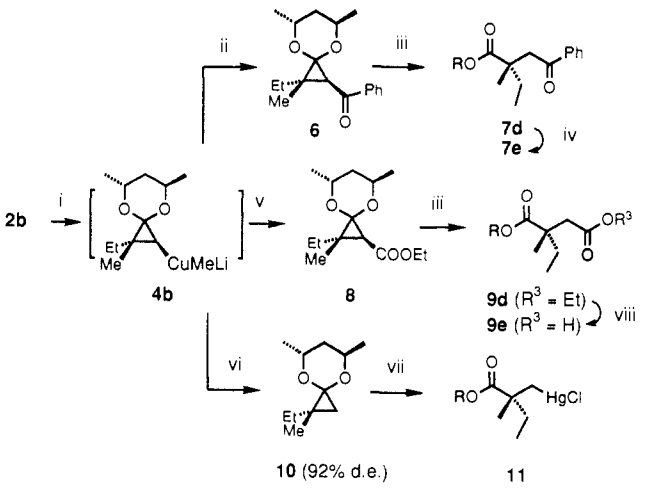
(8) Stereochemistry has been determined by conversion to (*R*)-2-methyloctanoic acid. See supplementary material for details.

Scheme II.[a]



[a] (i) Me_2CuLi; (ii) PhCOCl; (iii) H^+; (iv) PCC, then K_2CO_3/MeOH; (v) ClCOOEt, cat. $Pd(Ph_3P)_4$; (vi) MeOH; (vii) $Hg(OCOCH_3)_2$, then aqueous NaCl; (viii) PCC, then aqueous NaOH.

Thus, the addition of cuprates to **2b** gave **4b** with a diastereoselectivity of 90:10–96:4 (entries 6 and 7) (see below for structure determination), and the addition to **2c** gave **4c** with diastereoselectivities of 92:8–99:1 (entries 8–11).[9]

The cuprate **4b** serves as a unique nucleophilic synthon bearing a quaternary chiral carbon (Scheme II). For instance, electrophilic trapping of the cuprate **4b** with benzoyl chloride[10] gave ketone **6** as a single product, which upon treatment with aqueous HCl smoothly afforded γ-keto ester **7d** in 76% overall yield (based on **2b**). Removal of the chiral auxiliary under standard conditions[11] gave keto acid **7e** in 84% yield. Similarly, trapping of **4b** with ethyl chloroformate in the presence of a palladium catalyst[1] followed by acidic treatment afforded diester **9d** in 70% overall yield (based on **2b**). Conversion of **9d** to **9e**[12] established the absolute stereochemistry of **9d**, which in turn established the stereochemical course of the carbocupration reaction. Cyclopropylcarbonyl compound **8** can serve as a three-carbon component in the [3 + 2] cycloaddition route to γ-lactones.[13] The cyclopropanone ketal **10** obtained by proton quenching of **4** (89% yield, 92% d.e.) can also serve as a useful nucleophilic synthon. For instance, electrophilic ring opening of **10** with $Hg(OCOCH_3)_2$ in MeOH followed by treatment with aqueous NaCl gave an organomercurial **11** (79% yield), which can function as a chiral homoenolate synthon[14] under radical conditions.[15] The cyclopropylcuprates **3** and **4** would also be useful in the [3 + 2] and the [3 + 2 + 2] annulations reported previously for the achiral compounds.[1]

Examples of asymmetric synthesis using C_2-homochiral acetals are now abundant.[11,16,17] However, the present asymmetric in-

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duction differs from most of these reactions in that the carbon-oxygen bond of the acetal group is not cleaved during the reaction.[17] Studies are under way to clarify the mechanism of the asymmetric induction as well as that of the carbocupration reaction.

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Supplementary Material Available: Structure determination and physical properties of the cyclopropanes (8 pages). Ordering information is given on any current masthead page.

(17) Cf.: (a) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256. Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254. (b) Tamura, Y.; Kondo, H.; Annoura, H.; Takeuchi, R.; Fujioka, H. *Tetrahedron Lett.* **1986**, *27*, 81. (c) Jung, M. J.; Lew, W. *Tetrahedron Lett.* **1990**, *31*, 623.

An Antibody-Catalyzed Bimolecular Diels-Alder Reaction

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There exist over 1500 known enzymes which carry out a vast array of chemical reactions with remarkable specificity and reaction rates. It is surprising then that there are no documented examples of enzyme-catalyzed pericyclic cycloaddition reactions,[1] yet these are among the most powerful and commonly used reactions in synthetic organic chemistry. The most important of these is the Diels-Alder reaction of a diene with a dienophile, which provides a straightforward and highly stereospecific route to cyclohexene derivatives. In contrast to the majority of enzyme-catalyzed reactions, this reaction is believed to typically proceed through a concerted transition state involving the simultaneous formation of carbon-carbon bonds within a cyclic array of interacting orbitals.[2] Given the importance of this reaction in organic chemistry and its novel mechanism, it was of interest to ask whether a "Diels-Alderase" enzymelike catalyst could be evolved from an antibody combining site.[3]

Generation of antibodies to a structure that mimics the pericyclic transition state for a Diels-Alder reaction should result in an antibody combining site that lowers the entropy of activation $\Delta S^{\ddagger}$ by binding both the diene and the dienophile in a reactive conformation. The idea of using antibodies as "entropic traps" to lower the translational and rotational activation entropy of a reaction has been realized in antibody-catalyzed Claisen rearrangements[4] and in transacylation reactions.[5] This approach is particularly attractive for generating an antibody that catalyzes a Diels-Alder reaction since this reaction proceeds through a highly ordered transition state for which $\Delta S^{\ddagger}$ is typically on the order of -30 to -40 entropy units.[6] Recently, Hilvert and coworkers reported that antibodies generated against a stable bicyclic adduct resembling the product of the addition of a cyclic diene and dienophile catalyzed a Diels-Alder reaction.[7] Tetrachlorothiophene 1,1-dioxide was used as the diene since extrusion of sulfur dioxide from the Diels-Alder adduct minimizes product inhibition.

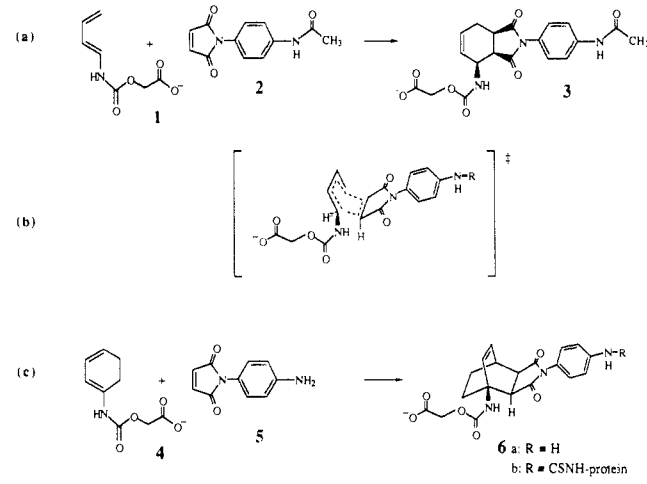

Figure 1. (a) Antibody-catalyzed Diels-Alder reaction. (b) Schematic representation of the transition state. (c) Synthesis of the transition-state analogue **6**.

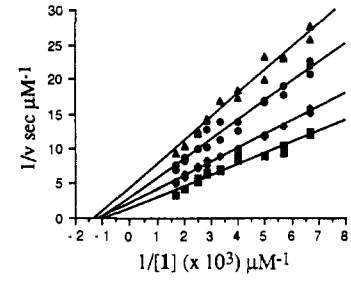

Figure 2. Lineweaver-Burk plot with the dienophile held at nine fixed concentrations while the diene was increased through nine distinct concentrations from 150 to 600 μM. All runs were performed in duplicate; only four lines are shown here for clarity (▲ = 150 μM 2, ● = 250 μM 2, ◆ = 350 μM 2, ■ = 600 μM 2. An analogous plot was also constructed with the diene held at fixed concentrations.

Our approach toward the design of a transition-state analogue (Figure 1) involves incorporation of an ethano bridge, which locks the cyclohexene ring of hapten **6** in a conformation that resembles the proposed pericyclic transition state[8] for the Diels-Alder reaction of cisoid diene **1** with dienophile **2**. As this geometry corresponds to a higher energy boat conformation of the product, it was anticipated that product inhibition would be minimized. Moreover, this design strategy is broadly applicable to Diels-Alder reactions involving acyclic dienes. We now report that antibodies generated to the transition-state analogue **6** catalyze the addition of the acyclic water-soluble diene **1** to the maleimide derivative **2** to give the cyclohexene product **3**.

Dienes **1** and **4** were prepared from the appropriate dienoic acid via formation of the acyl azide followed by a Curtius rear-

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