at 358.1 and 151.4 ppm for the carbyne and methylene carbons.[11] The presence of ^{13}C peaks at 265.8 and 240.7 ppm, but not near 230 ppm, suggested that the methylene group was bridging the iron atoms. An X-ray diffraction study[6] of **4** (Figure 2) confirmed this fact; otherwise the overall structure of **4** is remarkably similar to that of **2**. The methylene ligand bridges the two iron atoms only somewhat asymmetrically, however, especially compared to the weakly semibridging carbonyls of **2** and **4**. The structure of **5**, which like **1** exists as a mixture of cis and trans isomers, was confirmed by independent synthesis via photolysis of $Cp(CO)_2FeC(OMe)=CH_2$[12] and $MeCpMn(CO)_2(THF)$; it is apparently the first heterodinuclear μ-σ,π methoxyvinyl complex and only the second μ-methoxyvinyl compound of any kind.[13]

Thermal decomposition of **4** was complete in 20 h at 45 °C, giving as the only tractable products $[CpFe(CO)_2]_2$, **2**, and *methoxyvinyl compound* **6** *due to carbon–carbon bond formation between the carbyne and methylene ligands* (Scheme I). The structure of **6**[6] was confirmed by independent synthesis via the rapid room temperature reaction of $Cp(CO)_2FeC(OMe)=CH_2$ and $(cyclooctene)_2Fe(CO)_3$.[14] Carbonylation of **4** was cleaner but slower, being complete in 24 h at 75 °C or in 8 days at 45 °C, giving **5** (9%), **6** (4%), $MeCpMn(CO)_3$ (80%), $[CpFe(CO)_2]_2$ (60%), and **2** (16%). A much cleaner reaction took place between **4** and PPh_3 under similarly mild conditions, yielding methoxyvinyl cluster **7** as the major product (Scheme I). The timing of the PPh_3 incorporation into **7** is unknown, since **7** forms over the course of a few hours by room temperature reaction of PPh_3 with **6**. A crossover experiment involving reaction of **4** and its deuteriated bis-MeCp analogue $(\mu_3\text{-}COCD_3)(\mu_2\text{-}CD_2)(MeCp)_2Fe_2Mn(CO)_5$ (**8**-d_5) yielded as the only vinyl products **7** and its $MeCp/C(OCD_3)=CD_2$ analogue **9**-d_5.[15] *The* PPh_3*-induced ligand coupling is therefore intramolecular.*

In conclusion, we have demonstrated the stepwise and rational synthesis of a heterotrinuclear difunctional cluster and mild intramolecular *cluster*-mediated carbon–carbon bond formation. This is the first demonstration of intramolecular coupling via a crossover study in which the new fragment remains cluster-bound. The most closely related examples are due to Shapley, in which methylene–ketene coupling to give an η^4-oxaallyl fragment on a ruthenium cluster was induced by CO,[2a] and Dickson, in which methylene-μ,η^2-alkyne coupling to give an η^1,η^3-allyl fragment on a rhodium cluster occurred at room temperature.[2b] More typically, complete cluster destruction occurs,[2c-g] or in cases where the new fragment remains cluster-bound, the carbon–carbon bonds formed (such as in carbyne–carbyne coupling) lack stereochemical information.[2d,h-n] The coupling reaction described here, along with the metal atom "markers" inherent in the heteronuclear system, should permit kinetic and stereochemical studies that may shed light on the detailed mechanism. Such work is in progress.

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Supplementary Material Available: Spectroscopic data for **2** and **4**–**7** and tables of crystallographic data for **2** and **4** and details of the solutions (25 pages); tables of structure factors for **2** and **4** (19 pages). Ordering information is given on any current masthead page.

(11) For NMR data on *homo*nuclear iron and manganese μ-methylene compounds, see ref 10a and: (a) Herrmann, W. A.; Reiter, B.; Biersack, H. *J. Organomet. Chem.* **1975**, *97*, 245–251. (b) Herrmann, W. A.; Bauer, C. *Ibid.* **1981**, *204*, C21–C24. (c) Kao, S. C.; Lu, P. P. Y.; Pettit, R. *Organometallics* **1982**, *1*, 911–918.

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(14) Key data for **6** include two doublets in the ^1H NMR at δ 1.78 and 0.69 (J_{HH} = 4.4 Hz) due to the vinyl hydrogens and in the undecoupled ^{13}C NMR[13] a doublet of doublets at 35.4 ppm (J_{CH} = 153.6, 163.1 Hz) for the methylene carbon and most surprisingly a *quartet of triplets* at 241.7 ppm assigned to the quaternary vinyl carbon on the basis of long-range coupling to *both* the vinyl (J_{CH} = 4.6 Hz) and methoxy (J_{CH} = 3.0 Hz) hydrogens.

(15) The methoxy methyl was 99+% and the methylene 95.5% deuteriated in **8**-d_5. The initial crossover reaction mixture was 0.02 M each **4** and **8**-d_5 and 0.08 M PPh_3. The mixture of **7** and **9**-d_5 was analyzed by ^1H NMR; at 500 MHz, the methoxy signals are separated by 22 Hz, and the *E* and *Z* methylene hydrogens by 14 and 19 Hz, respectively. Greater than ~5% crossover at either the methyl or methylene site would have been detected.

Enzymatic Second-Order Asymmetric Hydrolysis of Ketorolac Esters: In Situ Racemization

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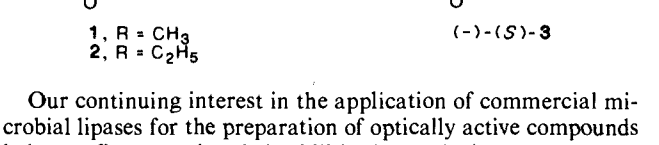
The enantiospecific hydrolyses of racemic carboxylic esters by hydrolytic enzymes are common biochemical procedures for the resolution of chiral carboxylic acids. As in all conventional resolution processes, enzymic or nonenzymic, the maximum obtainable yield of one pure enantiomer is 50%.

However, if a reaction could be conducted under conditions wherein the substrate may be racemized in situ, it should then be possible to transform the substrate completely to the desired enantiomeric pure product. This approach not only obviates the tedious recycling steps of the undesired remaining ester, but, more importantly, the enantiomeric excess of the product (ee_p) is now independent of the extent of conversion, *c*, and the process becomes apparently more enantiospecific.[1] This type of enzymatic second-order asymmetric transformation[2] has thus far only been achieved in a very limited number of cases in the amino acid field.[3] In this paper, we report the first successful application of this concept to the enzymatic asymmetric hydrolysis of carboxylic esters.

Ketorolac, 5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (**3**), is a compound of considerable therapeutic importance because of its potent antiinflammatory and analgesic activities.[4] More recently, it was reported that the (−)-*S* isomer of **3** is considerably more potent than the (+)-*R* isomer in animal studies.[5] The esters **1** and **2** were selected as model substrates for our enzymic studies, for we envisaged that the chiral center could be easily racemized under mildly basic conditions as a consequence of the resonance stabilization of the anion.



1, R = CH_3
2, R = C_2H_5

(−)-(*S*)-**3**

Our continuing interest in the application of commercial microbial lipases for the preparation of optically active compounds led us to first examine their abilities in catalyzing the enantios-

(1) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294. For example, the ee_p at 50% conversion of a conventional kinetic resolution with an *E* value of 10 is 0.67. Under in situ racemization conditions, the ee_p will remain at 0.82 throughout the conversion.

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Table I. Lipase-Catalyzed Hydrolyses of (±)-**1**

lipase	pH	time, h	ster pref	c[7]	ee[6] acid	ee[6] ester	E[7]
Mucor meihei[a]	8	22	*R*	0.489	94	90	101
Pseudomonas sp.[b]	8	40	*R*	0.508	90	93	65
Candida cylindracea[c]	8	44	*R*	0.560	74	94	23
Porcine pancrease[d]	8	87	*S*	0.111	32	4	2

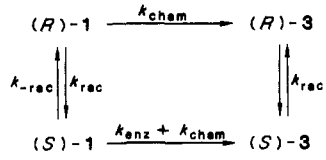
[a] Amino, MAP. [b] Boehringer, Mannheim. [c] Meito-Sangyo Ltd., OF-360. [d] Sigma Type II.

Table II. Protease-Catalyzed Hydrolyses of (±)-**1**

protease	pH	time, h	ster pref	c[7]	ee[6] acid	ee[6] ester	E[7]
Streptomyces griseus[a]	8	74	*S*	0.500	>96	>96	>100
Aspergillus saitoi[b]	6	312	*R*	0.455	96	80	>100
Bacillus subtilis[c]	8	74	*S*	0.392	96	62	97
Aspergillus oryzae[d]	8	74	*S*	0.578	70	>96	≥21

[a] Sigma Type XXI. [b] Sigma Type XIII. [c] Amano, Protease N. [d] Amano, Protease 2A.

Scheme I. Proposed Competing Reaction Pathways



pecific hydrolysis of (±)-**1**. Among some 15 lipases examined, several of these were found to be highly enantiospecific (Table I) but, unfortunately, they all preferentially cleaved the (+)-*R* ester (**1**). The only exception was the porcine pancreatic lipase (PPL), which exhibited low enantiospecificity (E = 2), This rather unexpected stereochemical outcome prompted us to continue our search for a suitable enzyme among the proteases. It is gratifying to note that in contrast to the lipases, most of the proteases have the desired *S* stereochemical preference. Some of these are listed in Table II. Particularly noteworthy is the protease of *Streptomyces griseus*, which exhibited very high enantiospecificity (E = >100). The availability of an enzyme with the required stereochemical features allowed us to proceed with the design of the in situ racemization experiment.

Our initial experiments were conducted in organic–aqueous biphasic media with trioctylamine as the base. Although complete conversion was achieved, the ee of the product was low and variable (ranging from 20% to 70%). This observation led us to induce the racemization in a purely aqueous alkaline medium, for the *S. griseus* protease is known to be stable at alkaline pH.

To achieve the desired objective, the following competing reaction kinetics (Scheme I) must be considered for the delineation of the precise experimental coonditions: (a) the rate of racemization (k_{rac}) should proceed faster than the rate of chemical hydrolysis (k_{chem}); (b) enzymatic hydrolysis (k_{enz}) of (*S*)-**1** should be much faster than racemization (k_{-rac}); (c) racemization of the acid ($k_{rac'}$) should not occur.

When (±)-**1** was exposed to *S. griseus* protease at pH 9.7, it was completely transformed to the acid (*S*)-**3** (ee = 0.76).[6] The 12% of the (*R*)-**3** formed is the result of both racemization ($k_{rac'}$) of (*S*)-**3** and competing nonenzymic hydrolysis (k_{chem}) of (*R*)-**1**, which indicates a low k_{rac}/k_{chem} ratio. While we made no attempts to suppress $k_{rac'}$ (e.g., by the precipitation of (*S*)-**3** as a salt), we were able to decrease k_{chem} or increase the ratio k_{rac}/k_{chem} by the use of the ethyl ester (±)-**2** as the substrate. The following procedure, developed after much experimentation, is presented to illustrate the feasibility of this catalytic process and its suitability for large-scale use: to 145 mg (0.51 mmol) of (±)-**2**, suspended in 35 mL of 0.2 M carbonate (HCO_3/NaOH) buffer (pH 9.7), was added 22 mg of *S. griseus* protease. The resulting suspension was stirred for 24 h at 22 °C. The reaction mixture was then extracted with CH_2Cl_2 to remove traces of remaining ester. Acidification of the aqueous layer to pH 2.0 resulted in the precipitation of (*S*)-**3**. The white precipitate was extracted into CH_2Cl_2. after the solution was dried over Na_2SO_4, the solvent was evaporated in vacuo to give 120 mg (92%) of (*S*)-**3** (ee = 0.85).[6] One crystallization (88 mg) from ethyl acetate–hexane (1:5) afforded 68 mg of (*S*)-(−)-**3** (ee = 0.94); $[\alpha]^{23}_D$ = −165° (*c* 0.85, MeOH).

It is noteworthy that the final step in the synthesis of Ketorolac[4] is the nonenzymic hydrolysis of its ester to yield the racemate (±)-**3**. In contrast, enzymatic second-order asymmetric hydrolysis of (±)-**2** allows one to obtain the eutomer[8] (*S*)-(−)-**3** of high optical purity at comparable chemical yields.

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(6) The enantiomeric excess (ee) of optically active **3** was determined by ^{1}H NMR measurement of its methyl ester in the presence of Eu(hfc)$_3$.

(7) The enantiomeric ratio (E value) is calculated from $E = [\ln [(1 - c)(1 - ee_s)]]/[\ln [(1 - c)(1 + ee_s)]]$, where $c = ee_s/(ee_s + ee_p)$. See ref 1 for a detailed discussion of these calculations.

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Nuclease Activity of 1,10-Phenanthroline–Copper Ion. Chemistry of Deoxyribose Oxidation

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The 1,10-phenanthroline–cuprous complex with hydrogen peroxide as a coreactant makes single-stranded breaks in B DNA in an oxidative reaction which is sequence dependent but proceeds at deoxyribose residues linked to any of the four bases, adenine, guanine, cytidine, and thymine.[1] The reaction efficiency at any sequence position depends on the stability of the $(OP)_2Cu^+$–DNA complex (step a of eq 1) adjacent to the deoxyribose attacked by the reactive copper–oxo species (I).[2,3]

$$(OP)_2Cu^+ + DNA \xrightarrow{\text{step a}} (OP)_2Cu^+\text{–DNA} \xrightarrow{H_2O_2} \underset{\text{I}}{(OP)_2Cu^{2+}\text{–oxo–DNA}} + OH^- \rightarrow \text{oligonucleotide products} \quad (1)$$

The proposed reaction scheme presented in Scheme I has been based on the analysis of products of the nucleolytic activity using uniformly labeled poly(dA-T),[4] 5′- and 3′-labeled restriction fragments,[5] and the self-complementary dodecamer 5-^{32}P-CGCGAATTCGCG as substrates.[6] These studies demonstrated the generation of free bases and 3′- and 5′-monophosphate ester termini. With the 5′ ^{32}P-labeled dodecamer, 3′-phosphoglycolates could be detected in minor amounts which varied with sequence position. In addition, an intermediate was trapped which did not comigrate with any known standards and converted to the 3′-phosphate upon treatment with piperidine or storage at −20 °C. In this paper, we report the isolation of 5-methylene-2-5*H*-furanone

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