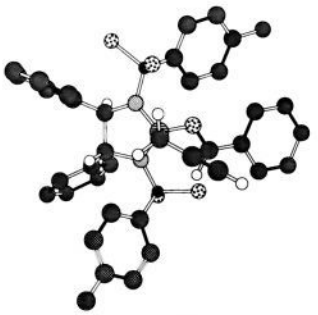
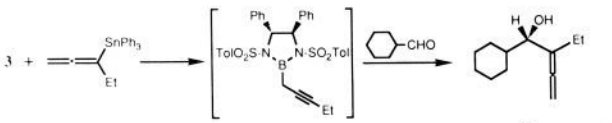
of this fact and also the many interesting transformations which can be foreseen for allenic alcohols of type **1**, for example, internal Diels–Alder reactions, Simmons–Smith methylenation, hydroboration, and other double bond addition reactions, this new methodology should prove valuable. The observed preference for absolute configuration **1** from the (*R*,*R*)-reagent **5** can readily be understood on the basis that assembly **6** is the most favorable arrangement for product formation; it also accords with previous observations on enantioselective carbonyl allylation.[2]



6

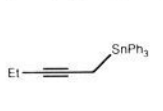
In order to demonstrate the extension of this carbonyl allenylation methodology to more alkylated systems, the stable, crystalline allenic tin reagent **7** was synthesized[8] and treated with bromoborane **3** (CH_2Cl_2, 0 °C, 5 h) to form reagent **8**. Reaction of **8** with cyclohexanecarboxaldehyde at −78 °C for 2.5 h afforded the adduct **9** in 78% isolated yield and 95% ee.[9] This result provides clear evidence for the broad generality of this new enantioselective allene synthesis.



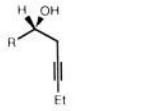
7 8 9 (2)

The scope of this approach has also been enlarged by the demonstration of its efficacy for the enantioselective propargylation of aldehydes, a process studied previously by H. Yamamoto using tartrate esters as controller groups.[10] 2-Propynyltriphenylstannane, mp 81–82.5 °C, readily prepared from propargylmagnesium bromide and triphenylchlorostannane in ether (71% yield),[11] upon treatment with bromoborane **3** in CH_2Cl_2 at 0 °C for 4 h and 23 °C for 10 min produced allenylborane **10** which reacted with a variety of aldehydes (Table II) to form propargyl carbinols **2**. The data in Table II allow the following conclusions: (1) excellent enantioselectivities are observed with the overall sense of chirality being that predicted by an assembly analogous to **6**, and (2) the process is effective for a variety of aldehydes in terms of isolated yield as well as enantioselectivity. In each case the chiral controller was easily separated from the propargylic alcohol **2** by precipitation from 3:1 ether–hexane at 0 °C for reuse,[7] and the pure alcohol was obtained simply by filtration of the soluble fraction through a short column of silica gel with use of 1:1 hexane–ether.

Enantioselective addition of the 2-pentynyl group to an aldehyde was selected for experimental study since this method would be ideal for the stereocontrolled synthesis of the third series of prostaglandins, e.g., PGE_3 and $PGF_{3\alpha}$.[12] The requisite organotin reagent 2-pentynyltriphenylstannane (**11**) was synthesized by



11



12 R n-C_5H_{11}
13 R (*E*)-$CH_3CH{=}CH$

reaction of the Grignard reagent from magnesium amalgam and 1-bromo-2-pentyne in ether with triphenylchlorostannane (84% yield of **11**, colorless liquid after filtration through silica gel deactivated with 2% Et_3N). Reaction of **11** with bromoborane **3** in CH_2Cl_2 (50 °C for 15 h) afforded the corresponding allenic borane which upon treatment with *n*-hexanal or crotonaldehyde at −78 °C for 2.5 h produced the (*S*)-carbinol **12** or **13** in 75–80% isolated yield and of 97–98% ee and >97% purity.[13] This highly successful result indicates a very practical solution to the long-standing problem of stereocontrolled synthesis of the PG_3 ω side chain.

In summary, this paper describes a new methodology for the enantioselective synthesis of alcohols of types **1** and **2** in a very efficient and practical way which promises to be widely useful.[14]

Supplementary Material Available: Detailed procedures are provided for the synthesis of **1** and **2** (R = n-C_5H_{11}), propadienyltri-*n*-butylstannane (**4**) and the triphenyl analogue, and 2-propynyltriphenylstannane, and key physical data (mp, IR, and ^1H NMR) are given for the chiral products listed in Tables I and II (5 pages). Ordering information is given on any current masthead page.

(8) The reagent **7** was prepared by the following sequence: (1) successive treatment of propargyl chloride with *n*-butyllithium in THF at −90 °C and triphenylchlorostannane to form 1-(triphenylstannyl)-3-chloro-1-propyne (91%); (2) reaction of this chloro compound with ethylmagnesium chloride and 1 equiv of CuBr in THF solution at −60 °C to form **7** (mp 75 °C, 87%). See: (a) Ruitenberg, K.; Westmijze, H.; Kleijn, H.; Vermeer, P. *J. Organomet. Chem.* **1984**, *277*, 227. (b) Ruitenberg, K.; Vermeer, P. *Tetrahedron Lett.* **1984**, *25*, 3019.

(9) Absolute configuration was assigned from the mechanistic model (assembly **6**).

(10) (a) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667.

(11) Le Quan, M.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1965**, 45.

(12) For previous syntheses of PG_3's see: (a) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490. (b) Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc.* **1984**, *106*, 3875.

(13) The main contaminant was the isomeric allene.

(14) This research was supported by the National Science Foundation and the National Institutes of Health.

Activation of Dioxygen by Bis(2,6-dicarboxylatopyridine)iron(II) for the Ketonization of Methylenic Carbons and the Dioxygenation of Acetylenes, Aryl Olefins, and Catechols: Reaction Mimics for Dioxygenase Proteins

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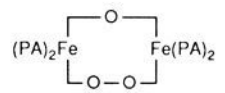
A recent study[1] has described the catalytic activation of excess hydrogen peroxide by bis(picolinato)iron(II) [$(Fe(PA)_2$] and (2,6-dicarboxylatopyridine)iron(II) [Fe(DPA)] for the efficient, selective ketonization of methylenic carbons and the dioxygenation of acetylenes and aryl olefins [the reactive intermediates have been postulated to be



and (DPA)FeOOFe(DPA)].[2] In contrast, the one-to-one combination of $Fe(PA)_2$ and HOOH results in Fenton chemistry with $(PA)_2Fe(OH)$ and $^{\bullet}OH$ the primary products.[3] Here we report

(1) Sheu, C.; Richert, S. A.; Cofrê, P.; Ross, B., Jr.; Sobkowiak, A.; Sawyer, D. T.; Kanofsky, J. R. *J. Am. Chem. Soc.* Accepted for publication.

(2) Cofrê, P.; Richert, S. A.; Sawyer, D. T. Submitted to *Inorg. Chem.*

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Table I. Ketonization of Methylenic Carbons and Dioxygenation of Aryl Olefins, Acetylenes, and Catechols via the $Fe^{II}(DPAH)_2$-Induced Activation of Dioxygen in 1.8:1 py/HOAc[a]

A. Cyclohexane (1 M); O_2 (1 atm, 3.4 mM)

$[Fe^{II}(DPAH)_2]$, mM	[reductant], mM	[products],[b] mM		reactn efficiency,[c] % (±3)
		c-C_6H_{10}(O)	c-C_6H_{11}OH	
8	0	1.1	<0.05	28
32	0	4.4	<0.1	28
83	0	10.4	<0.2	25
32	32 (PhNHNHPh)	9.9	<0.2	62
32	64 (PhNHNHPh)	15.4	<0.2	96 (4 turnovers; each 17% efficient)
3	10 (PhNHNHPh)	2.0	<0.1	133
3	100 (PhNHNHPh)	20.9	<0.2	1393 (67 turnovers; each 21% efficient)
32	16 (H_2NNH_2)	6.7	<0.2	42[d]
32	32 (H_2NNH_2)	9.1	<0.2	57[d]
32	32 ($PhCH_2SH$)	8.6	<0.2	54
32	128 ($PhCH_2SH$)	18.5	<0.2	116 (4 turnovers; each 23% efficient)
32	10 (H_2S)	5.5	<0.1	34 (1 turnover; 7% efficient)
32	62 (H_2S)	7.2	<0.2	45
14	225 (H_2S)	10.0	<0.2	143 (32 turnovers; each 35% efficient)

B. $Fe^{II}(DPAH)_2$ (32 mM); O_2 (1 atm, 3.4 mM)

substrate	products (mM)[b]	reactn efficiency,[c] % (±3)
c-C_6H_{12} (1 M)	c-C_6H_{12}(O) (4.4)	28
$PhCH_2CH_3$ (1 M)	$PhC(O)CH_3$ (3.5)	22
[+128 mM PhNHNHPh]	$PhC(O)CH_3$ [18.9]	
2-Me-butane (1 M)	$Me_2CHC(O)Me$ (1.0)	6
[+128 mM PhNHNHPh]	$Me_2CHC(O)Me$ [9.1]	
cyclohexene (1 M)	2-cyclohexen-1-one (1.2)	7
PhC≡CPh (0.6 M)	PhC(O)C(O)Ph (2.2)	14
c-PhCH=CHPh (1 M)	PhCH(O) (3.1)	10
1,2-$Ph(OH)_2$ (1 M)	HOC(O)CH=CHCH=CHC(O)OH (and its anhydride) (2.0)	13
PhCH(OH)C(O)Ph (0.3 M)	PhC(O)OH (5.2)	16
PhNHNHPh (100 mM)	PhN=NPh (100)	667[e]
$PhCH_2SH$ (128 mM)	$PhCH_2SSCH_2Ph$ (64)	800[e]
H_2S (128 mM)	S_8 (16.0)	800[e]

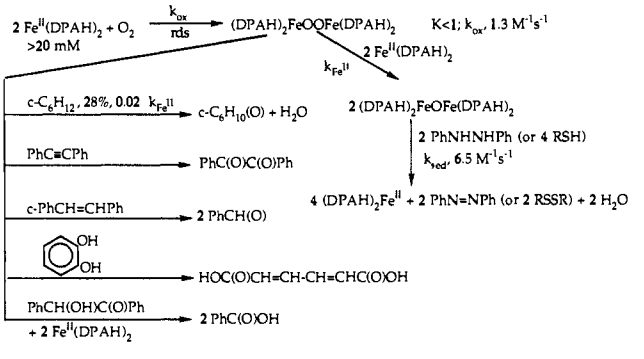
[a] Substrate and $Fe^{II}(DPAH)_2$ [$Fe(MeCN)_4(ClO_4)_2$ added to 2 equiv of $(Me_4N)_2DPA$] combined in 3.5 mL of pyridine/HOAc solvent (1.8:1 mol ratio), followed by the addition of 1 atm of O_2 (3.4 mM) in a reaction cell with 6 mL of head-space. Reaction time and temperature; 4 h at 22 ± 2 °C (for 3 mM $Fe^{II}(DPAH)_2$, the reaction time was 12 h). [b] The product solutions were analyzed by capillary gas chromatography and GC–MS (either direct injection of the product solution or by quenching with water and extracting with diethyl ether). [c] 100% represents one substrate ketonization or dioxygenation per $(DPAH)_2FeOOFe(DPAH)_2$ reactive intermediate. [d] More than 90% of the c-C_6H_{10}(O) underwent condensation with H_2NNH_2 to form the double Schiff base [(c-C_6H_{10})=NN=(c-C_6H_{10})]. [e] 100% represents one substrate oxidation per $(DPAH)_2FeOFe(DPAH)_2$ reaction intermediate.

that $Fe^{II}(DPAH)_2$ in the presence of O_2 (1 atm, 3.4 mM) and excess substrate is autoxidized to a reactive intermediate, which ketonizes methylenic carbons and dioxygenates acetylenes, aryl olefins, and catechols.

The produts and reaction efficiencies for various concentrations of catalyst [$Fe^{II}(DPAH)_2$] and substrates are summarized in Table I. The products are identical with those that result from the reactive intermediate formed from the combination of (DPA)FeOFe(DPA) and excess HOOH, (DPA)FeOOFe(DPA).[1] The dioxygenation of the substrates in Table I must result from a similar reactive intermediate. With cyclohexane, about one-fourth of the O_2 that is incorporated into the reactive intermediate reacts to give cyclohexanone as the only detectable product; the remainder oxidizes the excess $Fe^{II}(DPAH)_2$ to give $(DPAH)_2FeOFe(DPAH)_2$, which is catalytically inert.

In the absence of substrate the active catalyst is rapidly autoxidized to $(DPAH)_2FeOFe(DPAH)_2$ [4 $Fe^{II}(DPAH)_2$ per O_2; the apparent second-order rate constant, k_{ox}, has a value of 1.3 ± 0.5 M^{-1} s^{-1} ($k_{obs}/4$)].[4] The oxidized catalyst [$(DPAH)_2FeOFe(DPAH)_2$] is rapidly reduced to $Fe^{II}(DPAH)_2$ by PhNHNHPh, H_2NNH_2, $PhCH_2SH$, and H_2S (k_{red} = 6.5 ± 0.5, 0.6 ± 0.3, 0.5 ± 0.3, and 2.8 ± 0.5 M^{-1} s^{-1}, respectively) to give PhN=NPh, N_2, $PhCH_2SSCH_2Ph$, and elemental sulfur (S_8), respectively.[4] The PhNHNHPh reductant is an effective reaction mimic for the reduced flavin cofactors in xanthine oxidase and cytochrome P-450 reductase.[5]

Scheme I. Activation of O_2 by $Fe^{II}(DPAH)_2$ in 1.8:1 py/HOAc



The results of Table I and the close parallels of the product profiles to those for the (DPA)FeOFe(DPA)/HOOH/(py/HOAc) system[1] prompt the conclusion that the combination of $Fe^{II}(DPA)_2$ and O_2 results in the initial formation of the reactive intermediate [$(DPAH)_2FeOOFe(DPAH)_2$, **1**] via a rate-limiting step (Scheme I) and are the basis for the proposed reaction

(3) Sheu, C.; Sobkowiak, A.; Zhang, L.; Ozbalik, N.; Barton, D. H. R.; Sawyer, D. T. *J. Am. Chem. Soc.* **1989**, *111*, 8030.

(4) This chemistry has been monitored by UV–visible spectrophotometry, and the apparent reaction orders and rate constants have been determined from the initial rates of disappearance and appearance of $Fe^{II}(DPAH)_2$ (λ_{max}, 394 nm). The spectroscopic and redox characterization of this complex, $Fe^{II}(PA)_2$, and their oxidized forms [$(DPAH)_2FeOFe(DPAH)_2$ and $(PA)_2FeOFe(PA)_2$] are the focus of a detailed study.[2]

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pathways. Because K is less than unity, the yield of cyclohexanone increases linearly with $Fe^{II}(DPAH)_2$ concentration. The apparent rate for the ketonization reaction is proportional to substrate concentration, $Fe^{II}(DPAH)_2$ concentration, and O_2 partial pressure and increases with temperature (about five times faster at 25 °C than at 0 °C). Because the fraction of **1** that reacts with c-C_6H_{12} remains constant (~28%), the oxidation of excess $Fe^{II}(DPAH)_2$ by **1** must be a parallel process. Given that the ratio of concentrations [c-C_6H_{12}]/[$Fe^{II}(DPAH)_2$] is about 30:1 and the ratio of reactivities is 1:2.6, the apparent relative rate constant for reaction of c-C_6H_{12} and $Fe^{II}(DPAH)_2$ with **1** is about 0.02 $k_{Fe^{II}}$ assuming a stoichiometric factor of 2 for the latter).

Addition of PhNHNHPh, H_2NNH_2, $PhCH_2SH$, or H_2S to the reaction system [O_2/Fe(DPAH)$_2$/substrate in 1.8:1 py/HOAc] reduces the oxidized catalyst [$(DPAH)_2FeOFe(DPAH)_2$] and thereby recycles it for activation of O_2 to the reactive intermediate (Table IA). When 3 mM $Fe^{II}(DPAH)_2$ is used in combination with 100 mM PhNHNHPh, the rate for the ketonization of c-C_6H_{12} is reduced by an order of magnitude, but each cycle remains about 21% efficient with 67 turnovers within 12 h.

The dioxygenation of unsaturated α-diols (catechol and benzoin, Table IB) by the $O_2/Fe^{II}(DPAH)_2$ system parallels that of the catechol dioxygenase enzymes, which are non-heme iron proteins.[6] Hence, the reactive intermediate (**1**) of the $Fe^{II}(DPAH)_2/O_2$ reaction may be a useful model and mimic for the activated complex of dioxygenase enzymes.[7]

This system affords the means to the selective autoxidation (oxygenation) of hydrocarbon substrates (e.g., c-C_6H_{12}) via the coprocessing of H_2S (or RSH)-contaminated hydrocarbon streams. Thus, the combination of c-C_6H_{12} and H_2S with $Fe^{II}(DPAH)_2$ and O_2 in 1.8:1 py/HOAc yields c-C_6H_{10}(O) and S_8 (Table IA).

Acknowledgment. This work was supported by the National Science Foundation under Grant CHE-8516247 and the Welch Foundation under Grant A-1042 with a Robert A. Welch Graduate Fellowship (C.S.).

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Conformational Studies of *N*-Benzoyl-L-phenylalanine by Combined Rotation and Multiple-Pulse Spectroscopy ^1H Nuclear Magnetic Resonance

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A common feature encountered in amino acids, proteins, and polypeptides is the possibility of forming complex amorphous phases in the solid state through inter- and/or intramolecular hydrogen bonding, van der Waals, and electrostatic interactions.[1,2] This behavior has recently been examined by ^{13}C NMR studies of L-phenylalanine, which revealed that the dynamic and static properties of this amino acid in the solid state are influenced by the method of preparation.[3] Due to oligomerization and the formation of multicrystalline or amorphous domains, X-ray crystallographic data are only available for a few such cases. Limited by resolution and dipolar interaction of protons in solids, problems of this type have not previously been studied by observing the hydrogen bonded proton directly. Recent progress in combined rotation and multiple-pulse spectroscopy (CRAMPS) experiments has shown a dramatic improvement in sensitivity and resolution,[4] and in some diamagnetic solids, a proton resolution as high as ~0.2 ppm has been achieved.[5,6] Previously, the relationship between the inter-oxygen distance $R_{O\text{-}O}$ and proton chemical shift of -O-H···O= type H bonding was established by using the homonuclear proton-proton dipolar decoupling technique[7] of a series of carboxylic acid single crystals. The correlation was later repeated and improved for carboxylic acid polycrystalline samples with use of the CRAMPS technique.[6] Recently we have also obtained an empirical correlation, $R_{O\text{-}O}$ (Å) = 2.97 - 0.0276δ (ppm), from a series of amino acids and carboxylic acids for nearly linear -O-H···O=C bonds.[8] This relation is found to be valid also for polyaminopolycarboxylic acids such as DTPA, EGTA, and EDTA where the H-bonding network is more complicated.[8] We now show that ^1H CRAMPS experiments and the shift-distance correlation can be used to deduce the geometric parameters and possible conformations for various hydrogen bonded arrays of solid samples of *N*-benzoyl-L-phenylalanine (*N*-Bz-Phe).

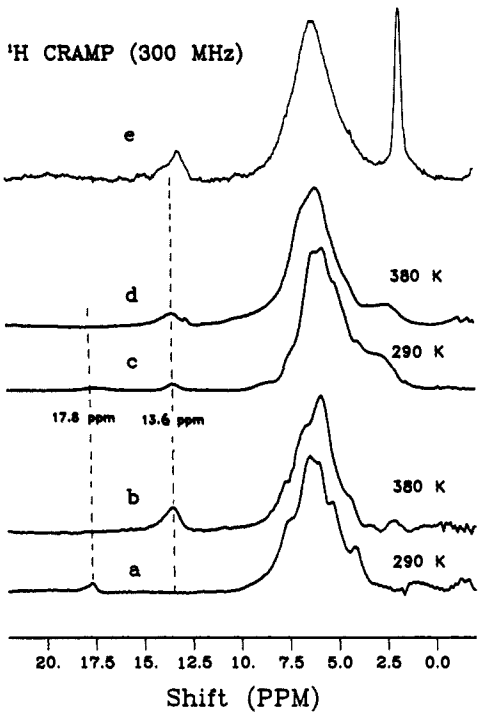

Figure 1. Proton CRAMPS spectra for *N*-benzoyl-L-phenylalanine for sample A (a, b), sample B (c, d), and sample C (e). Traces b and d correspond to the results after heating the samples to 380 °K. The sharp peak at 1.76 ppm in spectrum e is the adamatane internal reference.

Three samples of *N*-Bz-Phe were prepared by different methods. Sample A was crystallized from chloroform or triturated with hexane:ethyl acetate from acetone solution. Sample B was crystallized from water:ethanol, water:acetone, or hot water solution with slow cooling, and sample C was crystallized from hot water followed by rapid cooling to room temperature.[9] Shown

† Department of Chemistry.
‡ Center for Biological NMR.
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