With this latter consideration in mind, efforts are in progress to both improve selectivity and gain greater insight into the geometric constraints involved in oxygen atom transfer.

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Supplementary Material Available: Experimental data of the preparation and characterization of **1** and **2** and of all relevant precursors and details of the X-ray diffraction study of $\{\mathbf{1}\cdot[(CH_3)_2CO]_2\}\cdot(CH_3)_2CO$ and tables of atomic parameters, calculated hydrogen parameters, and distances and angles (22 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of Acids by the Palladium-Catalyzed Hydrocarboxylation of Olefins in the Presence of (*R*)-(−)- or (*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl Hydrogen Phosphate

Howard Alper* and Nathalie Hamel

Ottawa-Carleton Chemistry Institute
Department of Chemistry, University of Ottawa
Ottawa, Ontario, Canada K1N 6N5

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Metal complex catalyzed hydrocarboxylation (eq 1, R′ = H) and related hydroesterification reactions (eq 1, R′ = alkyl) of olefins are, together with hydroformylation, among the most extensively investigated processes in homogeneous catalysis.[1] Both

$$RCH{=}CH_2 + CO + R'OH \xrightarrow{MLn} RC(CORR)'HCH_3 + RCH_2CH_2COOR' \quad (1)$$

products of the hydrocarboxylation or hydroesterification of monoolefins are of considerable industrial value. For example, this methodology is of use in the synthesis of linear fatty acid esters, although stringent conditions are usually required.[2] Valuable representatives of branched-chain acids are 2-arylpropionic acids, which are the most important class of nonsteroidal antiinflammatory agents. A remarkably mild, completely regiospecific route to branched-chain acids was described in 1983, using palladium chloride as the catalyst under acidic conditions (eq 2).[3]

$$RCH{=}CH_2 + CO + H_2O \xrightarrow[PdCl_2,\ CuCl_2,\ HCl,\ \text{room temperature, 1 atm}]{O_2,\ THF,\ L^*} RC^*H(CH_3)COOH \quad (2)$$

While attempts have been made to achieve asymmetric hydrocarboxylation and hydroesterification, good enantioselectivity has yet to be realized.[4,5] Another problem has been the lack of regiochemical control, as these reactions are not regiospecific. Since the palladium chloride catalyzed process is regiospecific, and since the unsaturated group of the reactant is prochiral, then the use of an added chiral ligand can, in principle, result in the asymmetric synthesis of branched-chain acids. We now report the synthesis of acids in quite high optical purity, as well as good chemical yield, by the use of an appropriate chiral ligand for the palladium chloride catalyzed reaction.

Table I. Hydrocarboxylation of *p*-Isobutylstyrene (**1**) and 2-Vinyl-6-methoxynaphthalene (**2**)

substrate	L*	**1** (or **2**)/L*/$PdCl_2$	product yield,[a] %	optical yield,[b] %
1	(*S*)-BNPPA	7.7/0.38/1.0	89	83 (*S*)
	(*S*)-BNPPA	7.7/0.77/1.0	80	55 (*S*)
	(*R*)-BNPPA	7.7/0.38/1.0	81	84 (*R*)
2	(*S*)-BNPPA	4.2/0.42/1.0	46	72 (*S*)
	(*S*)-BNPPA	10/0.5/1.0	71	85 (*S*)
	(*R*)-BNPPA	4.2/0.42/1.0	48	76 (*R*)
	(*R*)-BNPPA	7.7/0.38/1.0	64	91 (*R*)

[a] Yield of pure material. [b] Determined by optical rotation measurements, relative to those for the pure enantiomers, reported in the literature[9,10] and confirmed by independent measurements of authentic pure *S*-(+) enantiomers in the authors' laboratory.

Two commercially important drugs are ibuprofen [2-(*p*-isobutylphenyl)propionic acid] and naproxen [2-(6-methoxy-2-naphthyl)propionic acid]. In both cases, it is the *S*-(+) enantiomer that is pharmacologically active.[6] The two olefinic precursors, *p*-isobutylstyrene (**1**) and 2-vinyl-6-methoxynaphthalene (**2**), were chosen as representative substrates in this investigation. The requisite olefins were easily prepared by nickel(II)-catalyzed cross coupling of a commercially available bromoarene with a Grignard reagent.[7] Specifically, treatment of *p*-bromostyrene with isobutylmagnesium chloride in the presence of (dppp)$NiCl_2$ afforded **1** in 76% yield. Similarly, 2-vinyl-6-methoxynaphthalene was isolated in 86% yield by (dmpe)$NiCl_2$-catalyzed reaction of 2-bromo-6methoxynaphthalene with vinylmagnesium bromide.

Reaction of *p*-isobutylstyrene (**1**) in tetrahydrofuran (THF) with carbon monoxide, water, oxygen, hydrochloric acid, palladium chloride, cupric chloride, and D-menthol as the added chiral ligand afforded pure ibuprofen in 94% yield, but the optical yield was only 2% (*S* configuration).[8] The ratio of **1**/D-menthol/$PdCl_2$ used was 10/3.8/1.0. Use of a 1/1 ratio of reactant to chiral ligand significantly reduced the acid yield and did not markedly affect the extent of asymmetric induction. Other chiral ligands including L-menthol, (*R*)-1,1′-bi-2-naphthol, D-diethyl tartrate (DET), and (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) were of little use here, affording acids in <10% optical yield under a variety of conditions.

Effective chiral resolving agents are the atropisomeric (*R*)-(−)- and (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNPPA). These compounds have been successfully employed for the resolution of a variety of pharmacologically useful organic bases[11,12] and helicenes (using HPLC).[13] It seemed conceivable that (*S*)-(+)- and (*R*)-(−)-BNPPA could function effectively in the acidic medium used for the hydrocarboxylation reaction. Indeed, use of (*S*)-(+)- and (*R*)-(−)-BNPPA as chiral ligands afford (*S*)-(+)- and (*R*)-(−)-ibuprofen, respectively, in 83–84%

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optical yield (see Table I for results). The best ratio of **1**/BNPPA is 20/1), with 10/1 giving inferior results. Similarly, naproxen was obtained in good yield and in up to 91% optical yield.

Let us compare this new asymmetric hydrocarboxylation reaction with several recent, metal-catalyzed approaches to optically active ibuprofen or naproxen. A higher degree of optical purity of (*S*)-(+)-naproxen was attained by BINAP–ruthenium(II)-catalyzed hydrogenation of 2-(6-methoxynaphthyl)-2-propenoic acid.[14] Unfortunately, a high pressure of hydrogen (135 atm) is required, and the acrylic acid derivative has to be synthesized via several steps. In 1987, Parrinello and Stille[15] described the use of a Pt(II) complex of (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine [(-)-BPPM], with $SnCl_2$, for the hydroformylation of **1**, **2**, and other olefins. While the percent enantiomeric excess of the formed aldehyde approaches 80%, the regioselectivity was poor, with an unfavorable branched/linear ratio (~0.5). Consequently, the chemical yields of the desired aldehydes were modest. Furthermore, hydroformylation of **1** and **2** required drastic conditions (2400 psi) and a subsequent oxidation step to produce the acids.

In summary, the hydrocarboxylation of olefins with BNPPA occurs under exceptionally mild conditions (room temperature, 1 atm), is completely regiospecific (linear acids were not formed), and affords acid in both high chemical and high optical yields.

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Registry No. 1, 63444-56-4; **2**, 63444-51-9; (*S*)-BNPPA, 124756-11-2; (*R*)-BNPPA, 124756-12-3; *p*-bromostyrene, 2039-82-9; *tert*-butylmagnesium bromide, 5674-02-2; 2-bromo-6-methoxynaphthalene, 5111-65-9; vinylmagnesium bromide, 1826-67-1; (*S*)-(+)-ibuprofen, 51146-56-6; (*R*)-(-)-ibuprofen, 51146-57-7; (*S*)-naproxen, 22204-53-1; (*R*)-naproxen, 23979-41-1.

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^{57}Fe Nuclear Magnetic Resonance Chemical Shifts of Hindered Iron Porphyrins. Ruffling as a Possible Mechanism for d-Orbital Energy Level Inversion

Lars Baltzer* and Marie Landergren

Department of Organic Chemistry
University of Göteborg and
Chalmers University of Technology
412 96 Göteborg, Sweden

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The discrimination of binding between carbon monoxide and oxygen in heme proteins has inspired the syntheses of porphyrins with one side hindered by, e.g., a "cap",[1] a "pocket",[2] a "strap",[3] a "basket handle",[4] or some other device for the purpose of obstructing the binding of ligands to one side of the porphyrin, but the properties of these model hemes have not led to a straightforward explanation of the natural regulatory mechanism. So far, there is only one demonstrated example of a model compound that exhibits a tilt of the CO relative to the heme normal in the solid state, the "pocket" porphyrin.[5] In the series of hybrid "basket-handle" porphyrins, for example, the effect of a decrease in the length of the aliphatic chain spanning one side of the porphyrin is not to increase the degree of tilt of the bound carbonyl but rather to increase the degree of ruffling[6] of the porphyrin core.[7] Among the heme proteins, myoglobin-CO exhibits a tilted CO and an almost flat porphyrin,[8] but in human carbonyl hemoglobin,[9] the tilt is very small and the porphyrin is clearly ruffled. Thus, the intriguing question of CO regulation still inspires investigations of heme proteins and heme models.

Table I. ^{57}Fe Nuclear Magnetic Resonance Chemical Shifts of Some Carbonyl Iron(II) Porphyrin Complexes in Toluene-d_8 at 25 °C

compd	δ, ppm	Δδ[a]
FePF(Bulm)(CO)	8110	+14
FeBH12(Bulm)(CO)	8036	+19
FeBH10(Bulm)(CO)	7728	-11
FeBH9(Bulm)(CO)	7500	-12
Fe(PPIX)(py-d_5)(CO)[b]	8205	
Fe(meso-PIX)(py-d_5)(CO)[b]	8188	
FePF(Bulm)(CO)[c]	8131	

[a] Effect on chemical shift of replacing axial Bulm with py. [b] Solvent is D_2O. [c] Solvent is DMF:H_2O, 90:10. PF is picket fence; BH is basket handle; 12, 10, and 9 indicate number of carbon atoms in superstructure; PPIX is protoporphyrin IX; meso-PIX is mesoporphyrin IX.

It follows that spectroscopic tools for the investigation of structure in these systems are of considerable interest. NMR techniques are often the natural first choice in such a case but the ^{1}H and ^{13}C NMR spectra are practically uninformative, with regard to the subtle details of porphyrin conformation, and the coupling constant $^1J_{Fe-C}$ does not vary significantly between the known complexes. The resonance Raman frequencies and the IR CO stretching frequency do vary[10] but not in an easily interpretable way, and the observed frequency shifts are very small. The UV/vis spectra do not provide any detailed structural information. In particular, the weak d–d transitions are not observable under the intense $\pi-\pi^*$ transitions.[11]

In this communication, we report that the ^{57}Fe NMR chemical shifts are extremely sensitive to deformation of the porphyrin geometry and that novel information about the electronic levels may be extracted from investigations of substituent effects on the chemical shift within the simple framework of the Ramsey equation. In the hybrid "basket-handle" porphyrins, the ruffling leads to large changes in the iron d-orbital energies that may be important in understanding ligand binding in heme proteins and models.

The ^{57}Fe NMR experiments were carried out on a Varian VXR 400 NMR instrument operating at 13.05 MHz, using 15-mm nonspinning sample tubes and a solenoid coil probe, with a 90° pulse width of 90 μs. The syntheses of "basket-handle" porphyrins were carried out according to the literature.[4] After reduction to the ferrous state, no paramagnetic material could be detected in the ^{1}H NMR spectra, the ^{57}Fe NMR chemical shift measurements were reproducible, and at the concentration of ferrous porphyrin used, 5 mM, the rate of electron transfer from trace amounts of ferric material would be too slow to affect the chemical shift measurements.

The factors affecting the ^{57}Fe NMR chemical shift (Table I) in iron porphyrins can be derived from a simple ligand-field argument.[12] A more electron releasing group on the porphyrin

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