Asymmetric Hydrogenation with New Chiral Functionalized Bisphosphine–Rhodium Complexes

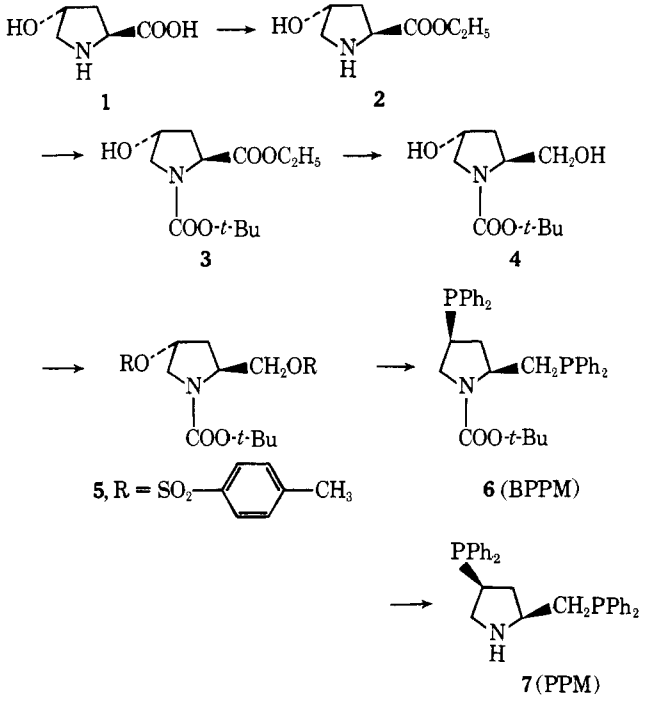
Sir:

Recent advances in catalytic asymmetric synthesis[1-5] have proven some chiral reagents useful commercially as well as of interest theoretically for the syntheses of optically active steroid hormones[1,2] and α-amino acids.[3-5] The available data[1-6] also have indicated that careful chiral reagent–substrate matching was needed to achieve high optical yields of the desired product.

We wish to describe here new chiral functionalized bisphosphine reagents, (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (PPM) (**7**) and (2*S*,4*S*)-*N*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM) (**6**), which consist of two phosphines as ligand functional groups for the metal and a third functional group (>NH or -NCOO-*t*-Bu) expected to fix the substrate conformation by means of its electronic interaction with the substrate functional groups.

The functionalized bisphosphines were synthesized from L-hydroxyproline (**1**) as shown in Scheme I.

Scheme I



Conventional esterification and butoxycarbonylation treatments of L-hydroxyproline (**1**) gave in a high yield the boc-ester (**3**),[7] oil, $[\alpha]^{20}_D$ − 67.8° (*c* 1.75, EtOH), which was then converted by reduction of the ester group with 1 molar equiv of lithium aluminum hydride in tetrahydrofuran followed by tosylation with tosyl chloride in pyridine to the ditosylate (**5**),[7] mp 155–156 °C, $[\alpha]^{20}_D$ −23° (*c* 0.4, benzene), in a high yield.

Subsequent reaction of **5** with sodium diphenylphosphine afforded the bisphosphine (**6**),[7] mp 104–105 °C, $[\alpha]^{20}_D$ −36° (*c* 0.6, benzene), in a good yield (50–60% overall yield from **1**). Further treatment of **6** with a excess of trifluoroacetic acid at 0 °C for 3 h gave the aminobisphosphine (**7**),[7a] viscous oil, $[\alpha]^{20}_D$ −5° (*c* 0.5, benzene), in a high yield.

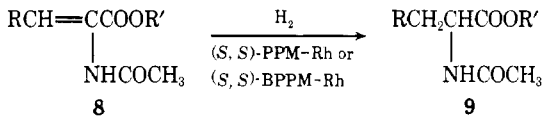
Hydrogenations of substituted cinnamic acids were carried out with a catalyst formed in situ from **6** or **7** and [Rh(1,5-hexadiene)Cl]$_2$. The hydrogenation products were isolated in 85–97% yield according to the procedure reported by Kagan et al.[4a] Table I shows the optical yields of substituted alanines

Table I. Asymmetric Hydrogenation of α-Acetamidoacrylic Acids[a]

Substrate	Chiral reagent	Solvent	Optical yield[c] (configuration)	
8a	PPM	EtOH	6	(*S*)
8a	PPM	EtOH[b]	6	(*S*)
8a	BPPM	EtOH-H_2O (2:1)	2	(*R*)
8a	BPPM	MeOH	30	(*R*)
8a	BPPM	EtOH-H_2O[b] (2:1)	48	(*R*)
8a	BPPM	MeOH[b]	83	(*R*)
8a	BPPM	EtOH[b]	91	(*R*)
8b	BPPM	EtOH	7	(*S*)
8b	BPPM	EtOH[b]	15	(*R*)
8c	BPPM	EtOH	32	(*R*)
8c	BPPM	EtOH[b]	83	(*R*)
8d	BPPM	EtOH[b]	86	(*R*)
8e	BPPM	EtOH[b]	87	(*R*)

[a] All hydrogenations were run with 2 mmol of substrate, 0.01 mmol of [Rh(1,5-hexadiene)Cl]$_2$, and 0.022 mmol of biphosphine in 15 ml of solvent at 20 °C for 20 h under initial hydrogen pressure of 50 atm. [b] 0.06 mmol of triethylamine was used. [c] Calculated on the basis of reported values for the optically pure compounds: (*S*)-**9a**, $[\alpha]^{26}_D$ +46.0° (*c* 1, EtOH), ref 4b; (*S*)-**9b**, $[\alpha]^{25}_D$ +21.4° (*c* 1.9, MeOH) (B. Zerner, R. P. M. Bond, and M. L. Bender, *J. Am. Chem. Soc.*, **86**, 3674 (1964)); (*R*)-**9c**, $[\alpha]^{19}_D$ −53.4° (*c* 1.8, EtOH) (S. Yamada, T. Fujii, and T. Shioiri, *Chem. Pharm. Bull.*, **10**, 680 (1962)); (*S*)-**9d**, $[\alpha]^{20}_D$ +40.8° (*c* 1, MeOH), ref 3c; (*S*)-9e, $[\alpha]^{27}_D$ +40.4° (*c* 0.5, H_2O) (R. R. Sealock, *J. Biol. Chem.*, **166**, 1 (1946)).

obtained under a variety of conditions for the following hydrogenation reaction.



8 **9**

8a,9a, R = phenyl; R′ = H
8b,9b, R = phenyl; R′ = CH_3
8c,9c, R = 3,4-methylenedioxyphenyl; R′ = H
8d,9d, R = 3-methoxy-4-acetoxyphenyl; R′ = H
8e,9e, R = 4-acetoxyphenyl; R′ = H

Table I shows clearly that BPPM-Rh complex behaves toward triethylamine in a manner substantially different from the features of DIOP,[4] ACMP,[3b] or BAPPE[3c]-Rh complex. In all experiments using BPPM, there was a remarkable effect of triethylamine on the optical yields. This effect may be interpreted on the basis of the conformational change of the chiral reagent-Rh complex and/or the much greater nucleophilicity of the carboxylate anion generated from the carboxyl and triethylamine.[8,9] In the case of PPM, the lack of effect of triethylamine added seems to suggest that the amino group of PPM interacted with the carboxyl group of the substrate as expected, but this interaction did not improve the optical yield. BPPM with triethylamine shows the highest optical specificity in ethanol rather than in methanol or in aqueous solution. These facts suggest that the novel interaction among BPPM-Rh, triethylamine, and the substrate which is more favorable in less polar protic solvent serves to produce 83–91% optical yields, but the plausible presentation of this interaction needs further investigation.[10]

BPPM is characterized as the best of the chiral phosphine ligands derived from naturally occurring chiral substances. Furthermore, it should be noted that (i) the starting material, L-hydroxyproline, is easily convertible into D-hydroxyproline[11] and (ii) modifications of the N-substituent and bisphosphine groups of PPM may be possible for the match of substrate

structure towards complete stereospecificity.

Further studies on these lines are under active investigation.[12]

References and Notes

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(3) (a) W. S. Knowles and M. J. Sabacky, *Chem. Commun.*, 1445 (1968); (b) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *J. Chem. Soc., Chem. Commun.*, 10 (1972); (c) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **97**, 2567 (1975).
(4) (a) T.-P. Dang and H. B. Kagan, *Chem. Commun.*, 481 (1971); *J. Am. Chem. Soc.*, **94**, 6429 (1972); (b) J. C. Poulin and H. B. Kagan, *J. Organomet. Chem.*, **91**, 105 (1975); (c) G. Gelbard, H. B. Kagan, and R. Sern, *Tetrahedron*, **32**, 233 (1976).
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(6) (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971; (b) J. W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974); (c) L. Marko and B. Heil, *Catal. Rev.*, **8**, 269 (1973); (d) R. E. Harmon, S. K. Gupta, and D. J. Brown, *Chem. Rev.*, **73**, 21 (1973).
(7) Satisfactory (a) spectral and (b) analytical data were obtained for this substance.
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(9) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Ann. N. Y. Acad. Sci.*, **172**, 232 (1970).
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(11) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Wiley, New York, N.Y., 1961, p 2037.
(12) The author thanks emeritus professor S. Yamada, University of Tokyo, for his encouragement.

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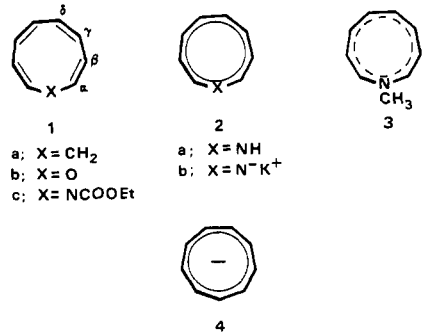
Received June 24, 1976

An Examination of the Heteronins by ^{13}C Nuclear Magnetic Resonance

Sir:

Careful analysis of a wide variety of physicochemical data recently secured in these laboratories has led to the classification of certain hetero[9]annulenes (heteronins)[1] as polyenic (**1**) and others as "aromatic" (**2**), while a third subgroup, namely the *N*-alkylheteronins, e.g., **3**, emerged as nondescript under the same criteria. In an attempt to more accurately probe the stereoelectronic changes attending the development of "aromaticity" in this family of π-excessive heterocycles, we have examined certain representative members by ^{13}C NMR and are now in position to offer description and interpretation of this information.



The ^{13}C NMR data (collected in Table I) were utilized to compare the various chosen members in terms of (i) chemical shift (a reliable measure of electron density) and (ii) ^{13}C–H coupling constant (a well-documented probe of hybridization). For obvious reasons, attention along these lines of comparison was focused primarily on the γ and δ carbons of each molecule, i.e., the two centers least likely to be influenced by direct interaction with the heteroatomic unit. The choice of models among available nine-membered rings proved to be straightforward with the heavily localized 1,3,5,7-cyclononatetraene (**1a**) elected as the "polyenic" reference and its well-delocalized anion **4**[2] chosen as the "aromatic" counterpart.

Table I.[a] ^{13}C NMR Constants of the Olefinic Centers of Select Heteronins and *cis*[4]-Cyclononatetraene

Compound	Temp[b] (°C)	Solvent	Chemical shift[c] (ppm)	Coupling constant[d] (Hz)	Assignment
1a	−37.0	Acetone-d_6	131.04	158	α
			128.70	~157	—
			128.56	~157	—
			128.36	~157	—
1b	−34.0	Acetone-d_6	141.33	193	α
			129.78	156	γ or δ
			124.26	159	γ or δ
			110.93	156	β
1c	−34.5	Acetone-d_6	130.13[e]	157	γ or δ
			127.92	157	
			125.87		—
			125.68		—
			125.28		—
			122.54[e]	156	β
			110.39	154	
2a	−34.5	Acetone-d_6	119.46	172	α
			117.76	152	γ or δ
			117.47	153	γ or δ
			100.48	155	β
	+30	Me_2SO-d_6	118.06	172	α
			116.86	152	γ or δ
			116.54	~152	γ or δ
			99.56	155	β
2b	+30	Me_2SO-d_6	124.09	154	α
			114.88	138	γ or δ
			112.68	142	γ or δ
			112.33	143	β
3	−34.5	Acetone-d_6	129.68	172	α
			122.31	153	γ or δ
			121.18	153	γ or δ
			101.22	156	β

[a] Spectra were uniformly recorded at 20 MHz on a Varian CFT-20 spectrometer equipped with a 5-mm probe. All determinations were made in vacuum-sealed NMR tubes; tetramethylsilane was employed as internal standard throughout. [b] Measured by thermocouple. [c] The term here denotes downfield shift from Me_4Si. [d] The values given refer to one-bond ^{13}C–H coupling. [e] The observed splitting is due to substituent-induced molecular asymmetry.

Since ^{13}C NMR chemical shift is primarily a function of electron density one may, in a molecule such as **1** (**2,3**), directly correlate properly chosen chemical shift differences with lone pair delocalization and hence the ability of a given member to realize its aromatic potential. In fact, bearing in mind that model **1a** ($\delta^3(\gamma,\delta)$ 128.54 ppm) has no available lone pair, while **4** (δ 109.5 ppm)[2] has a fully delocalized one[4] and assuming the relationship between ^{13}C chemical shift and electron density at carbon to be roughly linear, one may, for comparison purposes, readily translate chemical shift differences, $\Delta\delta(\gamma,\delta)$, between a given member of the family and **1a** or **4** into percent lone pair delocalization. Direct use of the chemical shift data collected in Table I thus yields $\Delta\delta(\gamma,\delta)$ terms which readily translate to ~8% lone pair delocalization in **1b** and **1c**, ~35% in **3**, ~58% in **2a**, and ~77% in **2b**.[4] Significantly, the observed increase of lone pair participation into the π system, on passing from **1b** or **1c** to **3** to **2a** and finally to **2b**, closely parallels the development of diatropic character previously deduced from ^1H NMR data.[1] In other words, when taken in conjunction with earlier ^1H NMR data the present ^{13}C NMR information