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N-CARBAMOYL-4-DIPHENYLPHOSPHINO-2-DIPHENYLPHOSPHINOMETHYLPYRROLIDINES(CAPP). EFFICIENT NEW CHIRAL LIGANDS FOR ASYMMETRIC HYDROGENATION

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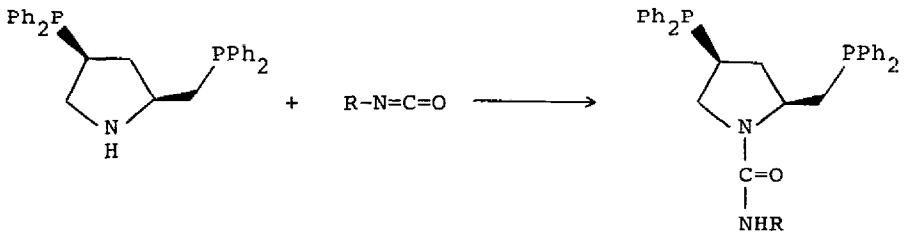
Summary: A series of N-(N'-substituted carbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidines (CAPP) was prepared, which exhibited excellent stereoselectivity in the asymmetric hydrogenation of α-acetamidocinnamic acid derivatives and itaconic acid as chiral ligand of the rhodium(I) catalyst.

Homogeneous asymmetric hydrogenation of olefins and carbonyl compounds catalyzed by rhodium complexes with chiral diphosphine ligands has been attracting much interest.[1] Among them, the stereoselectivity attained in the reaction of α-acylaminocinnamic acid derivatives has been shown to be particularly high.[1] Thus, this reaction is recognized as probe reaction for new chiral ligands. Although many chiral phosphine ligands have been developed, it has been shown that only a few ligands can achieve the excellent stereoselectivity of 95% enantiomeric excess (e.e.) and above. These are a) DIPAMP in the synthesis of N-acetylalanine (95.7% e.e.)[2] and methyl N-acetylphenylalanate (96% e.e.)[3], b) CHIRAPHOS in the synthesis of N-benzoylphenylalanine (99% e.e.)[4] and N-acetylleucine (100% e.e.)[4], c) BPPM in the synthesis of N-acetylalanine (98.5% e.e.)[5], d) BPPFOH in the synthesis of epinephrine hydrochloride (95% e.e.)[6], and e) PHELLANPHOS in the synthesis of N-acetylalanine (95% e.e.)[7].

In the course of our study on the mechanism of asymmetric hydrogenation and the crucial factors for effective asymmetric induction, we have recognized that a rigid structure of the chiral ligand is not necessarily a crucial factor, but some flexibility plays an important role, which enables "induced-fit" of the chiral metal complex molecule corresponding to the figures of substrates.[5,8] From this point of view, we synthesized a series of N-(N'-substituted carbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidines (CAPP), which have urea structure being able to act as intramolecular base for proton abstraction as well as intramolecular proton source and also as a stereo-controlling factor for the "induced-fit" action. Now, we describe here the new entry of excellent chiral diphosphines, CAPPs, some of which can achieve enantioselectiveties higher than 95% e.e. on being used as ligand of a rhodium complex catalyst in the asymmetric

hydrogenation of α-acetamidocinnamic acid derivatives.



a: R = C_6H_5, b: R = p-ClC_6H_4
c: R = p-BrC_6H_4, d: R = 3,4-$Cl_2C_6H_3$
e: R = p-$NO_2C_6H_4$, f: R = CH_3
g: R = CH_2=$CHCH_2$, h: R = c-C_6H_{11}

CAPP

A series of CAPPs were synthesized by a simple addition of isocyanates to PPM[9] which was derived from 4-hydroxyprolin. CAPPs are good crystalline compounds, very stable in air, and thus very easy to handle. A typical procedure is described for the synthesis of *methyl*-CAPP: To a solution of PPM (907 mg, 2.00 mmol) in chloroform (10 ml) was added methyl isocyanate (1.201 g, 2.10 mmol) in chloroform (10 ml) with stirring at ambient temperature under argon. The reaction completed within 10 min. After the solvent was evaporated, the residual solid was submitted to a short column chromatography on silica gel and colorless crystals of *methyl*-CAPP (939 mg, 92%) was obtained. Mp. 74-77°C, $[\alpha]_D^{25}$ -12.35° (c 0.502, benzene). Physical properties of CAPPs are listed in Table 1.

Table 1. Physical Properties of CAPPs[a]

	Ligand	Mp. (°C)	$[\alpha]_D^{25}$ [b]	IR (cm^{-1}) [c]	
				ν_{NH}	$\nu_{C=O}$
a	*Phenyl*-CAPP	180-183	-22.20	3270	1640
b	*p-Chlorophenyl*-CAPP	180.5-181.5	-13.99	3275	1640
c	*p-Bromophenyl*-CAPP	181-184	-10.45	3280	1640
d	*3,4-Dichlorophenyl*-CAPP	148-151	-10.77	3290	1645
e	*p-Nitrophenyl*-CAPP	103-106	- 4.19	3360	1655
f	*Methyl*-CAPP	74-77	-12.35	3330	1625
g	*Allyl*-CAPP	76-79	- 8.85[d]	3330	1625
h	*Cyclohexyl*-CAPP	79-82	-11.80	3330	1625

[a] Satisfactory elemental analyses were obtained for all CAPPs. [b] Measured in benzene, c 0.500-0.508. [c] Measured as KBr disk. [d] Measured in methanol, c 0.508.

Table 2. Asymmetric Hydrogenation Catalyzed by CAPP-rhodium Complexes[a]

CAPP	R	Catalyst Precursor	Optical Yield (% e.e.)[b]		
			1[c]	2[c]	3[d]
a	C_6H_5	I	95.4	95.6 (95.4)	95.4 (94.0)
		II	95.4	95.1 (96.1)	
b	p-ClC_6H_4	I	96.1	95.6 (93.0)	95.3 (94.4)
		II	95.4	92.3 (92.4)	
c	p-BrC_6H_4	I	97.4	95.2 (95.1)	93.5 (93.7)
		II	95.3	93.8 (92.1)	
d	3,4-$Cl_2C_6H_3$	I	97.9	90.9 (92.6)	94.0 (93.1)
		II	95.3	91.9 (92.8)	
e	p-$NO_2C_6H_4$	I	94.3	94.8 (94.7)	95.4 (95.0)
		II	95.7	95.3 (94.7)	
f	CH_3	I	94.5	92.5 (91.8)	93.8 (94.3)
		II	93.2	91.1 (91.6)	
g	CH_2=$CHCH_2$	I	90.6	91.3 (90.9)	93.5 (93.3)
		II	92.5	90.2 (91.2)	
h	c-C_6H_{11}	I	92.8	90.2 (89.6)	94.4 (94.5)
		II	93.2	90.7 (90.2)	

[a] All reactions were run with 2.50 mmol of substrate, 2.50×10^{-2}mmol (1.0 mol%) (for 1 and 2) or 1.25×10^{-2}mmol (0.5 mol%) (for 3) of rhodium catalyst under an atmospheric pressure of hydrogen. [b] Optical yields were determined on the basis of the reported maximum rotations: N-acetyl-(*S*)-phenylalanine methyl ester, $[\alpha]_D^{25}$ +15.9° (c 2.0, MeOH) (Ref. 11); N-acetyl-(*S*)-phenylalanine, $[\alpha]_D^{26}$ +46.0° (c 1.0, EtOH) (Ref. 4); (*R*)-methylsuccinic acid, $[\alpha]_D^{20}$ +16.88° (c 2.16, EtOH) (Ref. 12). Values in the parentheses are the optical yields on adding triethylamine: Et_3N/Rh = 2 for 1 and 2, Et_3N/Rh = 200 (Et_3N/substrate = 1) for 3. [c] Reactions were run at 25°C in 20 ml of ethanol unless otherwise noted. [d] Reactions were run at 25°C in 5 ml of benzene-methanol (1:3).

We carried out the asymmetric hydrogenation of α-acetamidocinnamic acid (1), methyl α-acetamidocinnamate (2), and itaconic acid (3) by using either neutral or cationic rhodium complexes with CAPPs, which were prepared *in situ* by reacting CAPP with $[Rh(COD)Cl]_2$ (I) (COD = 1,5-cyclooctadiene) or $[Rh(NBD)_2]^+ClO_4^-$ (II) (NBD = norbornadiene). Results are summarized in Table 2. As Table 2 shows, some of CAPPs can achieve the enantioselectivity higher than 95% e.e. It also turns out that i) enantioselectivity exhibited in these reactions are dependent upon the stereoelectronic nature of the substituent, R, in CAPP, and ii) addition of triethylamine causes only a slight change in enantioselectivity; the fact makes a sharp contrast to the case of BPPM.[9,10] These results imply that the carbamoyl moiety in CAPP acts as proton abstractor which generates the carboxylate anions of free acid substrates.

Further investigation along this line is actively under way.

REFERENCES AND NOTES

1. D. Valentine, Jr. and J. W. Scott, Synthesis, 329 (1978).
2. W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, J. Am. Chem. Soc., 97, 2567 (1975).
3. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, J. Am. Chem. Soc., 99, 5946 (1977).
4. M. D. Fryzuk and B. Bosnich, J. Am. Chem. Soc., 99, 6262 (1977).
5. I. Ojima and T. Kogure, Chem. Lett., 641 (1979).
6. T. Hayashi, A. Katsumura, M. Konishi, and M. Kumada, Tetrahedron Lett., 425 (1979).
7. M. Lauer, O. Samuel, and H. B. Kagan, J. Orgamometal. Chem., 177, 309 (1979).
8. I. Ojima and T. Kogure, Chem. Lett., 1145 (1978).
9. K. Achiwa, J. Am. Chem. Soc., 98, 8265 (1976).
10. I. Ojima, T. Kogure and N. Yoda, Chem. Lett., 495 (1979).
11. R. Glaser and B. Vainas, J. Organometal. Chem., 121, 249 (1976).
12. E. Berner and R. Leonardsen, Justus Liebigs Ann. Chem., 538, 1 (1939).

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