Table I. Electronic and Solvent Effects on Hydrocyanation Selectivity[a]

entry	R	selectivity (ee, %) 2-VN	MVN	solvent
1	Ph	46	40 (29)	benzene (THF)
2	3,5-$(CH_3)_2C_6H_3$	25	16	benzene
3	3,5-$(F)_2C_6H_3$	75	77	hexane
4a	3,5-$(CF_3)_2C_6H_3$	74	78	benzene[b]
4b	3,5-$(CF_3)_2C_6H_3$		85	hexane or C_6F_6[c]

[a] See Figure 1 for X, Y, and R; XY = OPh. 4,6-Hydroxyls were protected as the benzylidene acetal, R'-R' = PhCH. See footnote 7 for reaction protocol and analytical procedures. [b] 0.001 equiv of catalyst yielding 769 turnovers with 2.5 equiv of HCN in toluene. [c] 100% conversion (85% ee) for MVN with 2.5 equiv of HCN in C_6F_6.

selectivity of the reaction,[10b] substituents on the ligating phosphorus had a more pronounced effect. Several examples of these ligands derived from β-phenyl glucoside and their respective selectivities are shown in Table I. From this study, we found that *electron-withdrawing substituents on phosphorus-linked aryl groups dramatically enhance the enantioselectivity*. Such electronic effects of ligands on the enantioselectivity are rare, and as in the well-documented case of Mn(III)-mediated epoxidation reactions,[11] these may play an important role in the design of new catalysts. The highest enantioselectivities are obtained in nonpolar solvents ($C_6F_6 \approx$ hexane > benzene > THF), while increasing the reaction temperature decreases the enantioselectivity. Other factors such as the extent of reaction, Ni to substrate ratio, and ligand to Ni ratio[12] do not affect the observed enantioselectivity.

Remarkably, the highly enantioselective 3,5-$(CF_3)_2C_6H_3$ catalyst derivative also exhibits very high activity in the hydrocyanation of MVN. Catalytic activities as high as 552 turnover numbers/h (769 total) have been measured at 25 °C for the hydrocyanation of MVN using 0.13 mol % of this ligand and 0.1 mol % of Ni. By comparison, at 25 °C this catalyst is an order of magnitude more active than the commonly used NiP(*p*-$OC_6H_4CH_3)_4$ catalyst.[4,5] Using this catalyst, the naproxen precursor (*S*)-(−)-6-methoxy-2-naphthalene-2-propionitrile has been prepared in an optically pure form for the first time by recrystallization of the resulting product.[7]

Even though the enantioselectivity of our system has been optimized only for the naproxen precursor, we briefly investigated the selectivity in a number of other vinylarenes in the presence of the diphenylphosphinite ligand (R = Ph; XY = OPh) and the corresponding bis[bis(trifluoromethyl)phenyl]phosphinite derivative (R = 3,5-$(CF_3)_2C_6H_3$; XY = OPh). Listed below are the respective ee's for these ligands under our standard conditions: 4-isobutylstyrene, 10 and 50; 4-phenyl-3-fluorostyrene, 10 and 55; acenaphthylene, 0 and 59; 1-vinylnaphthalene, 63 and 68. In each case, the overall yield and the enantioselectivity with the electron-deficient phosphinite systems are unprecedented, and the unmistakable electronic effect on the ee has been confirmed.

Further studies on the asymmetric hydrocyanation reaction and applications of this ligand system in other reactions will be reported in due course.

Acknowledgment. We gratefully acknowledge the invaluable technical assistance of Mrs. M. S. Beattie, Ms. E. A. Duvall, and Ms. K. G. Messner.

Supplementary Material Available: Descriptions of typical experimental procedures for the synthesis of key ligands and hydrocyanation reactions (9 pages). Ordering information is given on any current masthead page.

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(12) Ligand to Ni ratios greater than 2 inhibit the hydrocyanation reaction.

Enantioselective Hydrogenation of the C=N Group: A Catalytic Asymmetric Reductive Amination Procedure

Mark J. Burk* and John E. Feaster

Contribution No. 6201
Central Research & Development Department
E.I. du Pont de Nemours & Company
Experimental Station, Wilmington, Delaware 19880-0328

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In contrast to the high enantioselectivities observed in both catalytic olefin[1] and keto group[2] hydrogenations, only limited success has been achieved in the catalytic asymmetric hydrogenation of the C=N group in compounds such as imines.[3] We recently described[4] a new homochiral series of 1,2-bis(phospholano)benzenes (Me-, Et-, and *i*-Pr-DuPHOS) and now demonstrate a unique and general application of these ligands in the rhodium-catalyzed asymmetric hydrogenation of the C=N group of *N*-acylhydrazones **1** (Scheme I).

Hydrogenation of the *N*-benzoylhydrazone of acetophenone (**1a**: R = R'' = Ph; R' = Me) proceeded readily under mild conditions (20 °C, 0.1 mol % catalyst, 1 atm of H_2, 1 h) using [(COD)-Rh(DuPHOS)]$^+CF_3SO_3^-$ as catalyst precursors. Of the three DuPHOS ligands, Et-DuPHOS proved to be superior in terms of enantioselectivity, providing the product *N*-benzoylhydrazine **2a** in 88% ee. Analogous rhodium catalysts bearing chiral phenylphosphines such as BDPP, CHIRAPHOS, and BINAP hydrogenate hydrazone **1a** relatively slowly, and with low enantioselectivity (9% ee, 23% ee, and 20% ee, respectively). The carbonyl function of the hydrazones **1** appears to be the crucial structural feature required for these hydrogenations to proceed; no hydrogenation was observed with either the *N*-phenylimine or the *N*-phenylhydrazone of acetophenone under the mild conditions used for hydrazones **1**. Substrate chelation to the cationic rhodium center most likely occurs initially via the carbonyl oxygen and the nitrogen of the hydrazone moiety. Complexes containing *N*-acylhydrazones which chelate in this fashion have been structurally characterized.[5]

In the hydrogenation of a series of *N*-aroylhydrazones **1**, 2-propanol was the best solvent found with respect to enantiose-

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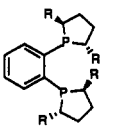

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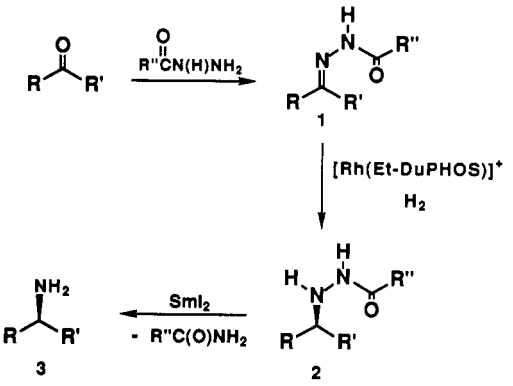
Table I. Rhodium-Catalyzed Asymmetric Hydrogenation of *N*-Aroylhydrazones **1**[a]

entry	R	R′	R″	temp (°C)	time (h)[b]	% ee,[c] confign[d]
1	C_6H_5	Me	C_6H_5	20	1	88, (*S*)-(−)[e]
2	C_6H_5	Me	*p*-$MeOC_6H_4$	20	2	91, (*S*)-(−)
3	C_6H_5	Me	*p*-$Me_2NC_6H_4$	20	2	92, (*S*)-(−)
4	C_6H_5	Me	C_6H_5	0	12	92, (*S*)-(−)
5	C_6H_5	Me	C_6H_5	0	12	92, (*R*)-(+)[f]
6	C_6H_5	Me	C_6H_5	−10	24	95, (*S*)-(−)
7	*p*-$MeOC_6H_4$	Me	C_6H_5	0	24	88, (*S*)-(−)
8	*p*-$EtO_2CC_6H_4$	Me	C_6H_5	0	12	96, (*S*)-(−)
9	*p*-$NO_2C_6H_4$	Me	C_6H_5	0	12	97, (*S*)-(−)[g]
10	*p*-BrC_6H_4	Me	C_6H_5	0	12	96, (*S*)-(−)[g]
11	C_6H_5	Et	C_6H_5	−10	24	85, (*S*)-(−)
12	2-naphthyl	Me	C_6H_5	0	12	95, (*S*)-(−)
13	CO_2Et	Me	C_6H_5	0	24	89, (*S*)-(−)[h]
14	CO_2Me	Et	C_6H_5	0	36	91, (*S*)-(−)[h]
15	CO_2Me	Ph	C_6H_5	20	36	91, *i*
16	Cy	Me	C_6H_5	−15	36	72, (*S*)-(+)

[a] Reactions were carried out at an initial H_2 pressure of 60 psi (4 atm) with 0.05–0.10 M 2-propanol solutions of substrate and the catalyst precursor [(COD)Rh((*R*,*R*)-Et-DuPHOS)]$^+$OTf$^-$ (0.2 mol %), unless otherwise noted. [b] Time allowed for complete conversion to product. Yields are essentially quantitative. [c] Enantiomeric excesses were determined on *N*-aroylhydrazines **2** by chiral HPLC (Daicel Chiralcel OJ or OB) as described in the supplementary material. [d] Absolute configurations for **2** were assigned by converting to the amines **3** and comparing the sign of optical rotation shown with that for the known amines. Optical rotations for the *N*-aroylhydrazines **2** are provided as supplementary material. [e] Reaction conducted at 15 psi of H_2 with 0.1 mol % catalyst. [f] The antipodal catalyst precursor [(COD)Rh((*S*,*S*)-Et-DuPHOS)]$^+$OTf$^-$ (0.2 mol %) was used. [g] Absolute configuration assigned on the basis of the sign of optical rotation and the order of HPLC elution in comparison with other *N*-benzoylhydrazines listed. [h] Absolute configuration established by hydrolysis of **2** (6 N HCl) to the α-hydrazino acid hydrochlorides and comparison of the sign of optical rotation with that for the known compounds. [i] Absolute configuration not established.

Scheme I. Asymmetric Catalytic Reductive Amination Procedure



lectivity (Table I). Replacing the para substituent of the *N*-benzoyl group (R″) of **1a** with more-electron-donating substituents such as *p*-MeO and *p*-Me_2N increased enantioselectivities to 91% ee and 92% ee, respectively, while the electron-poor *p*-NO_2 group led to a significant decrease in stereocontrol (24% ee). Such an electronic effect is consistent with coordination of the *N*-aroyl carbonyl group of **1a** to Rh. Lower temperatures afforded higher ee's (entries 1 and 4–6). We have examined substrate electronic effects with *N*-benzoylhydrazones derived from a series of para-substituted acetophenones (entries 4 and 7–10). Electron-withdrawing substituents (R and/or R′) on the hydrazone were found to favor higher enantioselectivities. Of particular interest are the *N*-benzoylhydrazines (**2**) derived from α-keto esters (entries 13–15); acid hydrolysis (6 N HCl, reflux) of **2** (R = Me, Et; R′ = CO_2Me) afforded the chiral α-hydrazino acid derivatives, which are known to be easily hydrogenolyzed to the corresponding α-amino acids.[6]

The (Et-DuPHOS)–Rh catalyst system exhibits a very high level of chemoselectivity in the hydrogenation of *N*-aroylhydrazones **1**. *Under the mild conditions required for quantitative hydrogenation of* **1a**, *little reduction* (*<2% for unfunctionalized alkenes and alkynes*) *or no reduction* (*ketones, aldehydes, esters, nitriles, imines, carbon–halogen, and nitro groups*) *of various functional groups was observed in competition experiments.* Such high chemoselectivity in reductions is rare[7] and in this case can be attributed to two factors: (1) substrate chelation which leads to faster relative rates of *N*-benzoylhydrazone hydrogenation, and (2) product inhibition; *N*-benzoylhydrazine **2a** was shown to inhibit the reduction of functional groups such as aldehydes, alkenes, and alkynes which are hydrogenated in its absence.

In order to enhance the synthetic utility of the asymmetric hydrazone hydrogenations, a method was required for transformation of the *N*-benzoylhydrazine products **2** into amines. We have found that reaction of **2** with samarium diiodide (≥2 equiv) leads to direct cleavage of the N–N bond and affords the desired chiral amines **3** along with benzamide[8] (Scheme I). While samarium diiodide is known to readily cleave certain heteroatom–heteroatom bonds,[9] reaction with 1,2-diphenylhydrazine has been shown to be relatively inefficient and slow.[10] In contrast, *reaction between* SmI_2 *and N-benzoylhydrazines* **2** *occurs almost instantaneously at 20 °C and proceeds with no loss of optical purity.* This simple method for N–N bond cleavage completes the convenient three-step asymmetric reductive amination process.

Current studies are aimed at expanding the scope of this process and elucidating the mechanism of enantioselection.

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Supplementary Material Available: Experimental details including procedures for hydrogenations, competition experiments, and samarium diiodide cleavage reactions, enantiomeric excess determinations, and optical rotations for **2** (9 pages). Ordering information is given on any current masthead page.

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(8) General procedure: To *N*-aroylhydrazine (**2**) in methanol was added a 0.1–0.05 M solution of samarium(II) iodide (2.2 mol at equiv). After 20 min, the reaction mixture was concentrated. The residue was acidified with 3 M HCl and extracted with diethyl ether to remove essentially all organic byproducts (i.e., benzamide). The aqueous layer was made basic with 3 M NaOH, extracted with diethyl ether, and concentrated to the amines **3** in 70–90% isolated yield.

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