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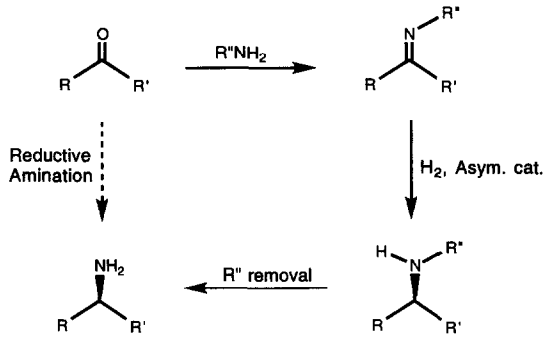
Catalytic Asymmetric Reductive Amination of Ketones via Highly Enantioselective Hydrogenation of the C=N Double Bond

Mark J. Burk*[1], Jose P. Martinez[1], John E. Feaster[2], and Nick Cosford[3]

1. Department of Chemistry, Duke University, P.M. Gross Chemical Laboratories, Durham, NC 27706
2. The DuPont Company, Central Research and Development, Experimental Station, Wilmington, DE 19880-0328
3. The DuPont Merck Pharmaceutical Company, Wilmington, DE 19880

Abstract: We describe a convenient, chemoselective asymmetric reductive amination procedure for the conversion of ketones to chiral hydrazines and amines. The key step in the three-step process is enantioselective DuPHOS-Rh-catalyzed hydrogenation of the C=N double bond of N-acylhydrazones. Detailed optimization studies revealed the effect of solvent, temperature, and the N-acyl group on the enantioselectivity and catalytic efficiency of the reaction. The reduction products, N-acylhydrazines, were converted to hydrazines or amines through hydrolysis or treatment with samarium(II) iodide, respectively.

Introduction. The ability to enantioselectively reduce the C=N double bond could lead to a useful reductive amination procedure for the conversion of prochiral ketones into optically active amino derivatives (Scheme 1). Such a process could entail first reacting a ketone with an amino-bearing reagent to provide an imine-like substrate. Subsequent enantioselective reduction, preferrably with hydrogen and an asymmetric catalyst, followed by removal of the amino protecting group (R"), would yield the desired primary amine in enantiomerically-enriched form. Given the great utility of optically active amines and amine derivatives in countless applications ranging from pharmaceuticals and agrochemicals to optoelectronic and membrane technology, the potential value of such a reductive amination procedure is readily apparent.

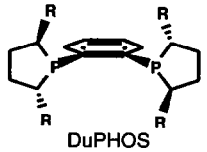


Scheme 1. Catalytic Asymmetric Reductive Amination Procedure

Relative to the high enantioselectivities and efficiencies observed in certain olefin[1] and keto group[2] reductions, catalytic asymmetric hydrogenation of the C=N double bond in compounds such as imines has met with limited success.[3] Fryzuk and James have reported a Rh catalyst based on use of the chiral diphosphine 1,2-bis(diphenylphosphino)-1-cyclohexylethane.[3a-c] Enantioselectivities as high as 91% ee were achieved in the hydrogenation of the N-benzylimine of 4-methoxyacetophenone. All other imine substrates, however, were reduced with much lower ee's. Bakos and coworkers[3d] described similar results in the hydrogenation of N-benzylimine acetophenone derivatives using a water-soluble Rh catalyst that contained sulfonated 2,4-bis(diphenylphosphino)pentane (BDPP) ligands. Both Osborn,[3f] and Spindler and coworkers,[3g] found that iridium catalysts bearing BDPP were moderately effective for hydrogenation of specific cyclic imine (80% ee) and acyclic imine (84% ee) substrates, respectively. Again, however, all other imines examined were reduced with much lower selectivity. Finally, Buchwald recently described a chiral titanocene catalyst that afforded enantioselectivities as high as 98% ee in the hydrogenation of certain cyclic imines.[3j] Acyclic imines, however, were hydrogenated with lower selectivities. Furthermore, high pressures (2000 psi) and high catalyst loadings (5 mol %) were required for high enantioselectivities and efficient catalysis.

Overall, an efficient, general, and highly enantioselective catalyst for hydrogenation of the C=N double bond remains elusive. Currently available catalysts which carry out asymmetric imine hydrogenations afford relatively high enantioselectivity with only specific imine substrates under optimized reaction conditions. Moreover, these catalysts tend to be rather inefficient, often requiring high catalyst loadings (S/C = 20-500), high H_2 pressures (40-130 atm) and long reaction times (up to 6 days). Efficient catalysts for enantioselective hydrogenation of other substrates containing the C=N double bond, such as hydrazones, oximes, or oxime esters have not yet been developed.

We recently reported the preparation of a new homochiral series of 1,2-bis(phospholano)-benzene ligands (DuPHOS; R = Me, Et, Pr, *i*-Pr) and described their use in highly enantioselective olefin hydrogenations.[4] In particular, enantioselectivities approaching 100% ee have been achieved in the DuPHOS-Rh-catalyzed hydrogenation of α-N-acylaminoacrylates enroute to a diverse range of α-amino acid derivatives.



DuPHOS

Herein, we now descibe the general utility of these ligands in the rhodium-catalyzed asymmetric hydrogenation of the C=N double bond in a series of N-acylhydrazones.[5] Detailed reaction optimization studies are outlined. These reductions were found to proceed with high levels of chemoselectivity. Also disclosed is a convenient method for converting the enantiomerically enriched N-acylhydrazine products to the corresponding amines via samarium diiodide-induced reductive N-N bond cleavage, thus completing a three-step catalytic asymmetric reductive amination procedure.

Results and Discussion

Substrate Chelation. Our research has focused on the development of a broadly effective catalyst for highly enantioselective hydrogenation of the C=N double bond. Optimally, an efficient (S/C ≥ 1000) and general catalyst which provides high rates and high enantioselectivities (≥90% ee) under mild conditions (25°C, ≤100 psi H_2) is desired. In order to accomplish these goals, we sought to employ the advantages associated with substrate chelation. Substrate chelation has been shown to be a critical element for the attainment of high enantioselectivities in enamide and enol acetate hydrogenations.[1b,4a,6] In addition to the functional group to be reduced, a substrate must contain a secondary donor group which can coordinate to the metal. For substrate generality in a reductive amination procedure such as that outlined in Scheme 1, it is desirable for the substrate to possess a secondary donor group which is not inherently part of the starting ketone or the final amine product. Therefore, we require a secondary donor group that is simple to introduce, and which is easy to remove from the product with no loss of enantiomeric purity.

The concepts of substrate chelation and secondary donor groups as they apply to C=N reductions are depicted in Figure 1. The success that we[4] and others have achieved in the asymmetric hydrogenation of olefinic substrates such as α-acetamidoacrylates[1,7] and enol acetates,[8] can be traced to a single common feature: the presence of a carbonyl oxygen which is three atoms removed from the double bond to be reduced. This carbonyl oxygen can, and does,[6] act as a secondary donor group which allows for chelation of the substrate to the catalyst metal center, as shown in the box (Figure 1). Substrate chelation can lead to: 1.) high enantioselectivities due the reduced number of degrees of freedom or approach geometries available to the substrate; and 2.) higher hydrogenation rates due to enhanced stability associated with intermediate metal complexes containing chelating olefins relative to non-chelating olefinic groups.[9] We previously have shown that this rate enhancement also can be used to obtain high regioselectivity and chemoselectivity in enamide[4b] hydrogenations. In our

efforts to tackle the asymmetric C=N hydrogenation problem, we noted that, like enamides and enol acetates, N-acylhydrazones **1** possess an amide-like carbonyl oxygen which is ideally situated three atoms from the double bond to be reduced (Figure 1). Thus, we attempted the enantioselective hydrogenation of N-acylhydrazones.

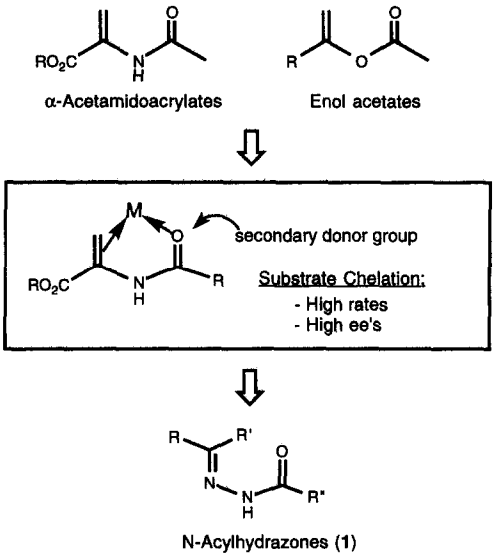
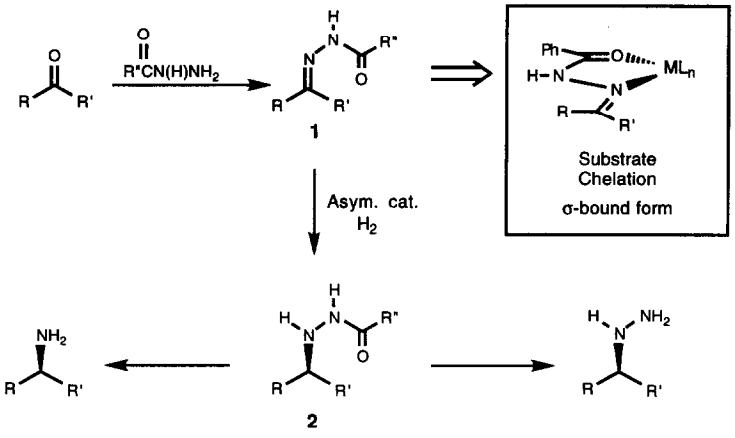


Figure 1. Substrate chelation and secondary donor groups in asymmetric C=N hydrogenations

N-Acylhydrazones. N-Acylhydrazones are readily prepared by treatment of a ketone with commercially available carboxylic acid hydrazides in the presence of an acid catalyst (Scheme 2).[10] We reasoned that N-acylhydrazones **1** may possess the correct arrangement of functionality to allow for chelation to a metal center. For example, the box in Scheme 2 depicts chelation of an N-benzoylhydrazone to a generic metal complex. The substrate is coordinated in a σ-bound form. In fact, complexes containing N-acylhydrazones which chelate in this fashion have been isolated and structurally characterized.[11] Subsequent enantioselective hydrogenation of coordinated N-acylhydrazones could provide enantiomerically-enriched N-acylhydrazine derivatives **2**, which then, hopefully, could be converted either to the desired free amines or free hydrazines with retainment of stereochemical purity.



Scheme 2. Asymmetric hydrogenation of chelating N-acylhydrazones **1**

Asymmetric Hydrogenation of N-Acylhydrazones 1

Initial Studies. We initially examined the asymmetric hydrogenation of the N-benzoylhydrazone of acetophenone (**1a**; R, R" = Ph; R' = Me) and found that cationic DuPHOS-rhodium complexes **3** (i.e., $[(COD)Rh(DuPHOS)]^+CF_3SO_3^-$)[4] are efficient catalyst precursors for this reduction under mild conditions (MeOH, 20°C, 0.1 mol % cat., 1 atm H_2, 1 h). Rhodium catalysts derived from the three ligands Me-DuPHOS, Et-DuPHOS, and *i*-Pr-DuPHOS, afforded the product **2a** with enantioselectivities of 57% ee, 72% ee, and 61% ee, respectively. As in our enamide hydrogenations,[4a] these studies indicated that Et-DuPHOS may be the superior ligand for this class of substrates. We, therefore, set out to optimize the efficiency and enantioselectivity of the reaction based on the Et-DuPHOS-Rh catalyst. All optimization studies were conducted with the substrate **1a**.

Optimization Studies

Solvent Effects. We have found that in the hydrogenation of substrate **1a**, the solvent effect can be substantial (Table 1). Our preliminary hydrogenations were performed in methanol where the Et-DuPHOS-Rh catalyst afforded the product **2a** in 72% ee. Moving to non-polar solvents such as toluene, or polar aprotic solvents such as EtOAc, THF or DMF, a significant decrease in ee was noted. Coordinating solvents such as DMF were observed to slow the reaction; hydrogenation of **1a** in DMF required 24 h for complete conversion to product. It appears that protic solvents such as alcohols are required for high enantioselectivity, but not for the reaction to proceed. The presence of large amounts of water led to lower selectivity (entry 6). Significantly, even among the alcohol solvents, large variations were observed. The most

dramatic difference occurred upon moving from methanol to ethanol and isopropanol where the enantioselectivities increased from 72% ee to 79% ee and 88% ee, respectively. Relative to isopropanol (88% ee), selectivities dropped upon using sterically more encumbered alcohols such as *tert*-butanol and 3-pentanol. Likewise lower ee's were observed with ethylene glycol and the more acidic fluorinated alcohols (entries 14-15).

Table 1. Solvent Effects in the Hydrogenation of **1a**[a]

Entry	Solvent	% ee
1	Toluene	7
2	EtOAc	9
3	THF	31
4	DMF [b]	51
5	CH_2Cl_2	53
6	MeOH/H_2O (1/1)	59
7	MeOH	72
8	EtOH	79
9	*i*-PrOH	88
10	2-Butanol (R or S)	86
11	t-BuOH	83
12	3-Pentanol	82
13	Ethylene Glycol	74
14	CF_3CH_2OH	69
15	$(CF_3)_2CHOH$	46

[a] Reactions were carried out at 25°C and an initial H_2 pressure of 60 psi (4 atm) with 0.05 M solutions of substrate and the catalyst precursor [(COD)Rh((*R,R*)-Et-DuPHOS)]$^+$OTf$^-$ (0.1 mol %). Reactions were allowed to proceed 2 h unless otherwise noted.
[b] Reaction required 24 h for complete conversion.

In terms of enantioselectivity, isopropanol is clearly the best solvent we have found to date. Solvent effects quite often are difficult to explain or interpret. This is no exception. The question is, why is isopropanol the solvent of choice? What role does isopropanol play and how does it to so dramatically influence the selectivity of the reaction? We reasoned that *i*-PrOH may possess the best combination of three properties: 1.) ability to coordinate to the metal center; 2.) correct steric environment; and 3.) hydrogen-bonding capability. In an attempt to determine whether coordination to the metal was important, we performed the hydrogenation of **1a** in both (*R*)-2-butanol and (*S*)-2-butanol. If coordination of alcohol to the metal during the enantioselectivity-determining step of the reaction was critical, chiral alcohols of opposite configuration should affect the selectivity of the reaction to different extents. Surprisingly, we found that hydrogenation of **1a** in either (*R*)-2-butanol or (*S*)-2-butanol using (*R,R*)-Et-DuPHOS-Rh afforded the product **2a** with the same selectivity (86% ee) and the same absolute configuration (*S*), irrespective of alcohol configuration. Based upon the results listed in Table 1, the enantioselectivities observed in reactions conducted in 2-butanol (86% ee) are exactly as one would predict through simple steric arguments.

In asymmetric catalysis, only small transition state energy differences are necessary to achieve high selectivity (on the order of 3.4 kcal/mol for 99% ee). Therefore, it is not surprising that changes in solvent may exhibit a remarkable effect on the enantioselectivity of many asymmetric reactions. It is clear that a better understanding of these effects is needed. The exact role that solvent is playing in our N-acylhydrazone hydrogenations remains uncertain. Regardless, isopropanol is currently the solvent of choice for these reactions.

Other Ligands and Catalysts. For comparative purposes, we have examined a variety of other potential catalysts for the asymmetric hydrogenation of **1a**. The results of these studies are listed in Table 2. Under the standard conditions where the Et-DuPHOS-Rh catalyst afforded **2a** in 88% ee over 1h, analogous chiral diphosphine-Rh catalysts performed uniformly poorly with respect to rates and enantioselectivities. For example, catalysts based on BDPP,[12] BINAP,[13] CHIRAPHOS,[14] DIOP,[15] and Ph β-Glup[16] provided the product with low relative rates and low enantioselectivites. Consistent with our studies (*vide infra*) which demonstrated the influence that ligand electronics can have on rates in these reactions, catalysts containing the phenylphosphines BINAP and DIOP only allowed conversions of 75% and 40% over 48 h and 60 h, respectively. Recently, we have found that the *n*-Pr-DuPHOS-Rh catalyst[4b] is slightly more effective than the Et-DuPHOS catalyst, yielding the product in 91% ee under identical conditions. The analogous cationic iridium catalyst bearing Et-DuPHOS was relatively inactive for the hydrogenation of **1a**, allowing only 7% conversion to product over 48 h. The neutral catalyst system based on the combination of Et-DuPHOS and $[(COD)RhCl]_2$ provided **2a** with lower selectivity (64% ee). The ee's in reactions with neutral catalysts were invariant with changes in solvent. Overall, the cationic Et-DuPHOS-Rh and *n*-Pr-DuPHOS-Rh catalyst systems appear to be uniquely suited to carry out these reductions with high enantioselectivities. Further improvements, however, were sought.

Table 2. Ligand/Catalyst Effects in the Hydrogenation of **1a**[a]

Ligand/Complex	% ee
Et-DuPHOS [b]	88
BDPP	9
BINAP [c]	20
CHIRAPHOS	23
DIOP [d]	20
Ph β-Glup	17
n-Pr-DuPHOS	91
$[(COD)RhCl]_2$ /Et-DuPHOS	64

[a] Reactions conducted using $[(COD)Rh(P)_2]^+OTf^-$ as catalyst precurser (0.1 mol %) in *i*-PrOH solvent at 25°C and initial H_2 pressure of 60 psi, unless otherwise noted. [b] 100 % conversion over 1 h. [c] 75 % conversion over 48 h. [d] 40 % conversion over 60 h.

Substrate Variations: N(H) Group of 1a. We have shown above that solvent changes can dramatically influence enantioselectivities in the hydrogenation of **1a**. In particular, solvents capable of hydrogen-bonding appear to be required for high selectivity. To test whether such hydrogen-bonding might involve interactions between the solvent and the N-H bond of N-benzoylhydrazone **1a**, we examined reduction of the N-methyl-N-benzoylhydrazone of acetophenone using the Et-DuPHOS-Rh catalyst in *i*-PrOH. Surprisingly, replacement of the N-H of **1a** with an N-Me group led to a significant drop in the selectivity to 8% ee. Although suggestive, this result does not conclusively demonstrate that loss of the hydrogen-bond donor capabilities of **1a** is responsible for the decrease in selectivity. This result, however, does indicate the importance of the substrate N-H group for high ee's. The nature of this importance remains to be clarified.

Substrate Variations: N-Acyl Group of 1a. The first N-acylhydrazone we examined as a substrate for enantioselective hydrogenation was the N-benzoylhydrazone of acetophenone (**1a**). Given our inital results, we envisioned that variation of the N-acyl group (R" of **1**) could potentially lead to higher enantioselectivities. We, therefore, have synthesized a series of acetophenone hydrazones (**1**) containing a wide variety of N-acyl groups. The hydrogenations were conducted using the Et-DuPHOS-Rh catalyst and some of these results are shown in Table 3. To our surprise and disappointment, no R" group was found which led to a substantial increase in the selectivity, and in fact, most led to lower ee's. For example, moving from the N-benzoyl group to N-acetyl, the enantioselectivity decreased from 88% ee to 53% ee. Likewise, the 2-furoyl and 2-methoxybenzoyl derivatives were reduced with lower selectivity. Little or no reduction was observed with N,N-o-phthaloyl, N-(1-naphthoyl), and N-tosylhydrazones. For the former two substrates, the observed lack of reduction may be due to the severely limited solubility of these compounds in alcoholic solvents (MeOH and *i*-PrOH).

Table 3. Selectivities vs N-Acyl Group (R") of **1a**[a]

Entry	R" of 1a	% ee
1	C_6H_5	88
2	CH_3	53
3	2-furoyl	76
4	2-$MeOC_6H_4$	58
5	4-$MeOC_6H_4$	91
6	4-$Me_2NC_6H_4$	92
7	4-$NO_2C_6H_4$	24

[a] Reactions performed at 25°C and 60 psi H_2 in 2-PrOH using Et-DuPHOS-Rh catalyst (0.1 mol %).

In an effort to glean some information from this study, we examined the effect of changing the electronic properties of the phenyl substituent R" through *para*-substitution (entries 5-7). 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 resulted in a significant decrease in stereocontrol (24% ee). Such an electronic effect is consistent with coordination of the N-aroyl carbonyl oxygen of **1a** to Rh during the enantioselectivity-determining step of the reaction. The more electron-rich nature of the *p*-MeO and *p*-Me_2N derivatives presumably facilitates interaction between the carbonyl oxygen and the metal, and produces a tightly bound chelating substrate with reduced conformational mobility. Accordingly, the low ee's obtained with the *p*-nitro derivative are indicative of a weak C=O-Rh interaction. Restricting the conformational mobility of substrates (via chelation) is well known to enhance selectivity in asymmetric catalysis.[1,2a] To our knowledge, this is the first example which demonstrates that enantioselectivites in asymmetric hydrogenations can be enhanced through variation of the electronic properties of the substrate secondary donor group.

Substrate Variations: Electronic Effects. In order to examine the effect of varying the electronic nature of the substrate, we have prepared N-benzoylhydrazones derived from a series of *para*-substituted acetophenones. Under our standard conditions (Et-DuP-Rh cat., 25°C, *i*-PrOH, 60 psi H_2) we found that electron-withdrawing substituents on the phenyl group favor higher enantioselectivities (Table 4). This observation appears general, and applies to all substrates examined to date (*vide infra*).

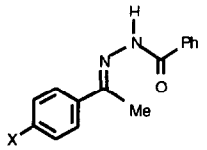


Table 4. Selectivities vs *para*-Substitution in **1a**[a]

Entry	X	% ee
1	OMe	79
2	$SiMe_3$	84
3	H	88
4	Br	92
5	CO_2Et	93
6	NO_2	93

[a] Reactions performed at 25°C and 60 psi H_2 in 2-PrOH using Et-DuPHOS-Rh catalyst (0.1 mol %).

A similar electronic effect has been observed in rhodium-catalyzed asymmetric olefin hydrogenations.[1b] The selectivity-enhancing effect of electron-withdrawing susbtituents in olefin hydrogenations can be attributed to greater π-back bonding from metal d-orbitals to the low energy π*-orbitals of electron-poor olefins. Stronger π-back bonding should lead to tigher binding, shorter M-olefin bond lengths, and reduced conformational mobility of the substrate. Combined, these factors lead to higher selectivity. Whether such π-backbonding arguments apply to these C=N hydrogenations remains an open question (*vide infra*). Currently, it is unclear whether slippage of the initial C=N σ-bound intermediate to a C=N π-bound intermediate is required for subsequent insertion into the M-H bond.

Reaction Parameters. Using the standard substrate **1a**, the effect of varying several reaction parameters was examined with respect to the enantiomeric purity of the product **2a**. No quantitative rate information has yet been obtained.[17] While the selectivities showed little apparent dependency on concentration (0.13-0.01 M in substrate), pressure (10-100 psi) or percent conversion, significant temperature effects were observed. Under otherwise standard conditions, the (Et-DuPHOS-Rh)-catalyzed hydrogenation of **1a** in *i*-PrOH was conducted at temperatures ranging from 50°C to -10°C (Table 5). Upon lowering the temperature, the enantioselectivites smoothly increased, and the product **2a** was obtained in 95% ee at -10°C. The positive effect of lower temperature was general for these hydrazone hydrogenations; all substrates examined to date were hydrogenated with higher selectivities at lower temperature. Qualitatively, the reaction rates decreased upon lowering the temperature; this probably reflects both a lowering of the inherent reaction rate, as well as the reduced solubility of the crystalline substrate **1a** in *i*-PrOH at these temperatures. In many cases, reaction rates dropped precipitously at temperatures below -10°C due to poor substrate solubility.

Table 5. Temperature Dependence of Enantioselectivity in Hydrogenation of **1a**[a]

Temp (°C)	Time (h)[b]	% ee
50	0.5	78
20	1	88
0	12	92
-10	24	95

[a] Reactions performed with **1a** at 60 psi H_2 in 2-PrOH using the Et-DuPHOS-Rh catalyst (0.2 mol %). [b] Time allowed for complete (100%) conversion.

Asymmetric Hydrogenation: N-Benzoylhydrazones. We have examined the enantioselective hydrogenation of a range of N-benzoylhydrazone substrates (**1**, R" = Ph) under our optimized conditions ((*R,R*)-Et-DuPHOS-Rh catalyst (0.2 mol %), *i*-PrOH, 0°C to -15°C, 60 psi H_2). The results of these studies are shown in Table 6. As can be seen, enantioselectivities up to

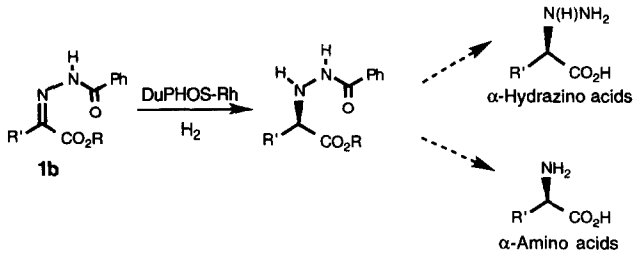
Table 6. Rhodium-Catalyzed Asymmetric Hydrogenation of N-Benzoylhydrazones **1**[a]

Entry	R	R'	Temp. (°C)	Time (h)[b]	% ee[c], config[d]
1	C_6H_5	Me	-10	24	95 (*S*)-(-) [e]
2	C_6H_5	Me	-10	24	95 (*R*)-(+) [f]
3	*p*-$MeOC_6H_5$	Me	0	12	88 (*S*)-(-)
4	*p*-$EtO_2CC_6H_4$	Me	0	12	96 (*S*)-(-)
5	*p*-$NO_2C_6H_4$	Me	0	12	97 (*S*)-(-) [g]
6	*p*-BrC_6H_4	Me	0	12	96 (*S*)-(-) [g]
7	C_6H_5	Et	-10	24	85 (*S*)-(-)
8	C_6H_5	CH_2Ph	-10	24	84 (*S*)-(-)
9	C_6H_5	CF_3	20	2	51 (*R*)-(-)
10	2-Naphthyl	Me	0	12	95 (*S*)-(-)
11	CO_2Et	Me	0	24	89 (*S*)-(-)
12	CO_2Me	Et	0	36	91 (*S*)-(-) [h]
13	CO_2Me	C_3H_7	0	36	90 (*S*)-(-) [h]
14	CO_2Me	C_6H_{13}	0	36	83 (*S*)-(-) [g]
15	CO_2Me	Ph	0	36	91, *i* [g]
16	$P(O)(OEt)_2$	Ph	-10	48	90, *i*
17	Cy	Me	-15	36	72 (*S*)-(+)
18	*i*-Pr	Me	-10	36	73 (*S*)-(+)
19	*t*-Bu	Me	20	48	45 (*S*)-(+)
20	Et	Me	-10	36	43 (*S*)-(+) [g]

[a] Reactions were carried out at an initial H_2 pressure of 60 psi (4 atm) with 0.05-0.10 M isopropanol 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 the known amines. Optical rotations for the N-aroylhydrazines **2** are provided as supplementary material. [e] Reaction conducted at 15 psi 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 based on sign of optical rotation and order of HPLC elution in comparison with other N-benzoylhydrazines listed. [h] Absolute configuration established by hydrolysis of **2** (3 N HCl) to the α-hydrazino acid hydrochlorides and comparison of the sign of optical rotation with the known compounds. [i] Absolute configuration not established.

97% ee were achieved in these reductions. In general, substrates containing aryl and methyl substituents (R = aryl, R' = Me) were consistently reduced with high selectivity. Substitution on the Me group tended to afford somewhat lower ee's (entries 7-9).

We were particularly interested in N-benzoylhydrazones **1b** (R = CO_2R) derived from α-keto esters (Scheme 3). Highly enantioselective reduction of these substrates could provide a convenient route to α-amino acid derivatives, as well as valuable α-hydrazino acid derivatives which exhibit interesting biological properties,[18] and are useful as α-amino acid surrogates in peptidomimetic research.[19] Current routes to α-hydrazino acids rely on stoichiometric use of chiral starting materials[20] or chiral auxiliaries.[21] We found that this substrate class may be hydrogenated with high enantioselectivity using the Et-DuPHOS-Rh catalyst (Table 6, entries 11-15). Moreover, arylglycines and their hydrazino analogues constitute an important class of compounds which are present in a plethora of natural and synthetic products of therapeutic interest.[22] While arylglycines are not accessible through catalytic asymmetric enamide hydrogenations, our enantioselective hydrazone hydrogenations are potentially well-suited for this application. The parent N-benzoylhydrazinophenylglycine derivative (**2**, R = CO_2Me; R', R" = Ph) was obtained in 91% ee using our Et-DuPHOS-Rh-catalyzed hydrogenation (Table 6, entry 15).



Scheme 3. α-Amino acids and α-hydrazino acids via N-benzoylhydrazone hydrogenations

Another interesting class of substrates are the analogous phosphonate ester-substituted hydrazones (**1**, R = $P(O)(OR)_2$). These reduction products may serve as intermediates for the preparation of α-hydrazino- and α-amino phosphonate esters. Like α-hydrazino acids, α-hydrazino- and α-amino phosponates are valuable α-amino acid mimics that display interesting biological activity.[23-24] A prototypical substrate (R = $P(O)(OEt)_2$, R' = Ph) was hydrogenated in 90 % ee with the Et-DuPHOS-Rh catalyst (Table 6, entry 16).

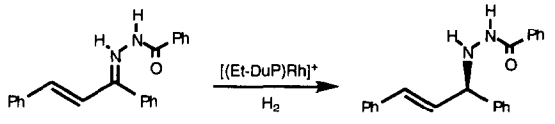
N-Benzoylhydrazones that contain only alkyl substituents (**1**; R,R' = alkyl) proved to be the most difficult substrates examined with respect to enantioselectivity (Table 6; entries 17-20). Even here, respectable selectivities could be achieved at low temperatures. For example, hydrazones substituted with cyclohexyl and methyl or isopropyl and methyl substituents were hydrogenated in 72% ee and 73% ee, respectively. Moving to the more sterically encumbered t-Bu group, however, both the rate and selectivity decreased (entry 19). One of the more difficult situations in asymmetric catalysis is when a chiral catalyst must differentiate between Me and Et groups of a

prochiral substrate. Using the Et-DuPHOS-Rh catalyst at -10°C, the hydrazone derived from 2-butanone was hydrogenated in 43% ee (entry 20).

The absolute configurations of the hydrogenation products **2** were very predictable for a given catalyst. In all cases examined to date, the (*R,R*)-Et-DuPHOS-Rh catalyst afforded the products **2** of (*S*)-absolute configuration, while the antipodal (*S,S*)-Et-DuPHOS-Rh catalyst yielded (*R*)-**2** with identical enantiomeric excess (with the exception of entry 9 where the symmetry label of the product changes from (*S*) to (*R*) due to the higher priority of the CF_3 group).

Chemoselectivity. An interesting and potentially useful property of the Et-DuPHOS-Rh catalyst system is the high level of chemoselectivity exhibited in the hydrogenation of N-benzoylhydrazones **1**. Competition experiments were conducted with mixtures (1:1 mole ratio) of hydrazone **1a** and a functional compound. *Under the mild conditions required for quantitative hydrogenation of* ***1a****, little or no reduction of various functional groups was observed.* No reduction of ketones, aldehydes, esters, nitriles, imines, carbon-halogen (F, Cl, Br), and nitro groups occurred under these conditions. Functional groups which possess the ability to strongly coordinate to the Rh center, such as nitriles and imines, did slow the hydrogenation, but were not reduced themselves. Significantly, less than 2% reduction of internal or terminal alkenes and alkynes occurred under the same conditions. For example, virtually complete chemoselective reduction of **1a** was observed in the presence of equimolar amounts of alkynes such as diphenylacetylene, 4-octyne, and 1-octyne, and alkenes such as cyclohexene, α-methylstyrene, allylbenzene, and 1-octene.

Hydrogenation of the N-benzoylhydrazone of chalcone (**4**) was examined as an example of internal chemoselectivity (Scheme 4). Hydrogenation of **4** with the Et-DuPHOS-Rh catalyst at 25°C proceeded smoothly, and again with essentially complete chemoselectivity in favor of hydrazone reduction (no reduction of the olefinic group was observed by ^1H and ^{13}C NMR). In contrast to the high chemoselectivity observed in this case, enantioselectivity was disappointingly low (25% ee). Such low selectivity is probably due to the similarity of the two groups flanking the hydrazone moiety in terms of steric and electronic properties.



4

Chemoselectivity: >95%
Enantioselectivity: 25% ee

Scheme 4. Intramolecular chemoselective hydrogenation of N-benzoylhydrazones

Such high chemoselectivity in reductions is rare[25] and in this case can be attributed to two factors:

1.) The primary factor responsible for high chemoselectivity is likely *substrate chelation* which leads to faster rates for N-benzoylhydrazone hydrogenation relative to other functional

groups (Figure 2, No. 1). Substrate chelation probably initially takes the form of a σ-bound intermediate. In Figure 2, we have shown this intermediate in equilibrium with a species containing a C=N π-bound substrate. Whether or not slippage of the σ-bound substrate to such a π-bound form is required for subsequent insertion into the Rh-H bond remains an open question. For example, one could invoke a mechanism involving the equivalent of a 1,3-hydrogen shift from Rh to the σ-bound substrate. Little information regarding the nature of intermediates in imine hydrogenations is available. Recent mechanistic work by Fryzuk and Piers suggests that a π-bound imine is required for insertion into the Rh-H bond of binuclear rhodium hydride complexes.[26]

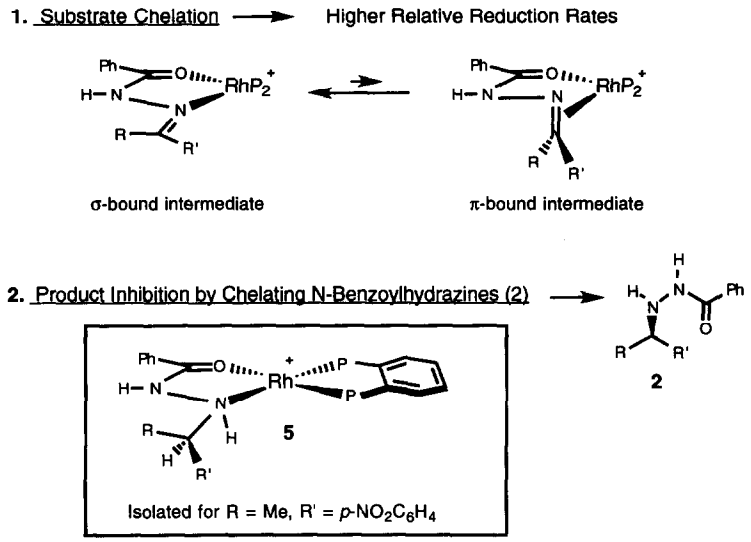


Figure 2. Factors responsible for high chemoselectivity in N-benzoylhydrazone hydrogenations

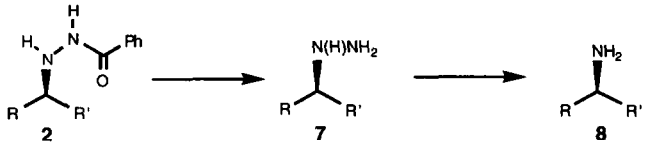
One argument favoring a π-bound intermediate in our system is based on the steric effects observed during hydrogenation of dialkyl-substituted hydrazones (Table 6, entries 17-20). Moving from the Cy and *i*-Pr-substituted hydrazones to the *t*-Bu-substituted derivative, we observed a significant decrease in the rate and selectivity of the hydrogenation. Molecular modeling suggests that steric interactions between the *t*-Bu group and the DuPHOS ligand would be minimal in a σ-bound intermediate, and no more significant than for the Cy and *i*-Pr substituted substrates. In contrast, in the π-bound form of the substrate, substantial steric interactions occur between the substituents and the ligand. Such unfavorable steric interactions could manifest themselves by increasing Rh-hydrazone bond distances to the point of making π-coordination difficult, thus lowering both rates and selectivities.

2.) The second factor responsible for such high chemoselectivity in this system is *product inhibition* by the N-benzoylhydrazine **2a** formed in the reaction (Figure 2, No. 2). Control

experiments showed, as expected, that the Et-DuPHOS-Rh catalyst was capable of hydrogenating assorted unsaturated compounds such as aldehydes, alkenes and alkynes. Under otherwise identical conditions, the addition of as little as 0.2 equivalents **2a** (per mole of functional substrate) was found to inhibit reduction of these functional groups. Like the substrate **1a**, the product **2a** has the correct arrangement of functionality (carbonyl C=O and hydrazine N) to allow for chelation to the Rh center. That the products **2** can behave as chelating ligands has been ascertained by our ability to isolate and spectroscopically characterize the Et-DuPHOS-Rh complex **5** containing the hydrogenation product N-benzoyl-*p*-nitrophenethylhydrazine (Figure 2, No. 2). Complex **5** was formed by the addition of the N-benzoylhydrazine product to the bis(methanol-d_4) solvate [((S,S)-Et-DuPHOS)Rh(CD_3OD)$_2$]$^+$OTf$^-$ (**6**; ^{31}P NMR (CD_3OD): δ 95.5 (s, J_{RhP} = 205 Hz)). Particularly informative was the ^{31}P NMR spectrum of the new N-benzoylhydrazine complex **5** which exhibited two pairs of doublet of doublets (^{31}P NMR (CD_2Cl_2): δ 88.11 (dd, J_{RhP} = 196.8 Hz, J_{PP} = 44.8 Hz), 98.19 (dd, J_{RhP} = 179.3 Hz, J_{PP} = 44.8 Hz)). The observed coupling pattern is similar to that observed in square planar chiral diphosphine Rh complexes containing enamide substrates.[6,27]

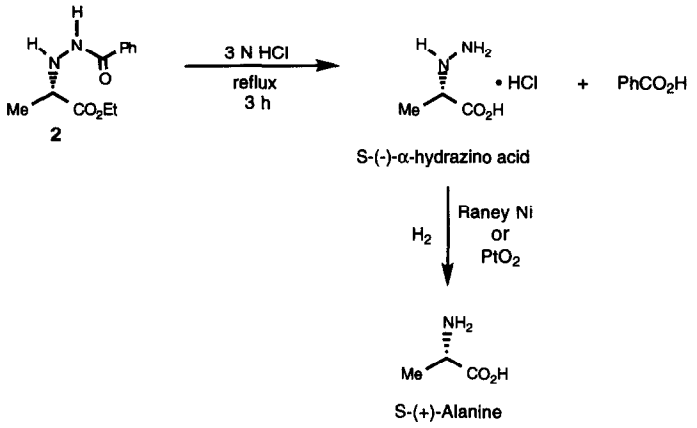
Most functional groups apparently do not compete well with the N-benzoylhydrazine products **2** for rhodium coordination sites. Fortunately, no significant autoinhibition was observed in these hydrogenations. The chelating hydrazone substrates **1** evidently are strong enough ligands to favorably compete for coordination sites, thus allowing the reaction to proceed at qualitatively uniform rates throughout.

Synthetic Utility: Conversion to Free Hydrazine and Amines. In order to enhance the synthetic utility of the asymmetric hydrazone hydrogenations, a method was required for conversion of the N-benzoylhydrazine products **2** into free hydrazines **7** and amines **8** with no degree of racemization (Scheme 5). Since various methods exist for the transformation of hydrazines to amines, we first focused on liberation of the free hydrazines **7**.



Scheme 5. Conversion of N-benzoylhydrazines (**2**) into free hydrazines (**7**) and amines (**8**)

Hydrolysis. One method for the production of **7** from **2** is simple hydrolysis of the N-benzoyl group. Our interest in the preparation of α-amino acid mimics led us initially to attempt hydrolysis of N-benzoylhydrazino esters. For example, we have found that ethyl (*S*)-2-(N-benzoylhydrazino)propionate (91% ee) may be hydrolyzed through the use of 3N HCl to afford (*S*)-(-)-2-hydrazinopropionic acid hydrochloride in high yield (91%), along with benzoic acid (Scheme 6). Little racemization occured during the hydrolysis step in this case. Hydrogenolysis of chiral α-hydrazino acids using Raney Ni (or PtO_2) to provide the corresponding α-amino acids is well-documented,[21a-c] and in the case at hand, affords (*S*)-(+)-alanine.

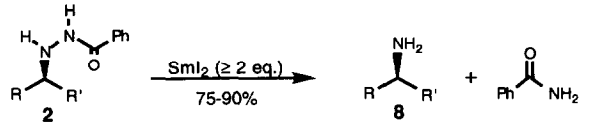


Scheme 6. Hydrolysis of the N-benzoyl group of hydrazone hydrogenation products **2**

Further investigation of the hydrolytic cleavage process, however, revealed that while N-benzoylhydrazines **2** which possess alkyl and/or ester substituents maintain stereochemical integrety to a large extent, hydrazones that bear aryl substituents are racemized readily under the hydrolytic conditions. This observation led us to seek alternative methods of N-N bond cleavage.

Samarium(II) Iodide. For the synthesis of amines, we desired a reagent which could directly cleave the N-N bond of the hydrazines **2** to provide the product in a single step. Searching the literature for heteroatom-heteroatom bond cleavage reactions, we found scattered reports of SmI_2-induced reductive cleavage. For example, SmI_2 has been shown to rapidly cleave the N-O bond of isoxazoles to yield enamino ketones,[28] and the O-O bond of peracids and peroxides to afford the corresponding acids and alcohols after hydrolysis.[29] In a more pertinent example, Kagan[30] demonstrated cleavage of the N-N bond of 1,2-diphenylhydrazine to provide aniline (after hydrolysis). While this reaction was slow (4 days) and inefficient (55% yield), we decided to employ SmI_2 for cleavage of the N-N bond of N-benzoylhydrazines **2**.[31]

We have found that SmI_2 does indeed induce reductive cleavage of the N-N bond of N-benzoylhydrazines **2** to afford, upon hydrolysis, the desired amines in 75-90% yield, along with benzamide (Scheme 7).



Scheme 7. Samarium(II) iodide-induced cleavage of the N-N bond of N-benzoylhydrazines **2**

In contrast to the slow reaction with 1,2-diphenylhydrazine, *reaction between SmI_2 and N-benzoylhydrazines **2** occured almost instantaneously at 20°C.* Furthermore, all N-benzoylhydrazines (**2**) examined, including aryl-substituted hydrazines, were cleaved to the amine products **8** with no loss of enantiomeric purity. For example, N-benzoylhydrazine **2a** (89% ee) was subjected to the SmI_2 cleavage conditions and was converted to α-phenethylamine which analyzed at 89% ee (chiral capillary GC; Cyclodex B, 80°C). Experimentally, the reaction is convenient and simple to perform, and entails treating a MeOH solution of N-benzoylhydrazine **2** with a THF solution of SmI_2 (1.0-0.5 M, 2.2-3 eqs.). Upon addition, the blue color of the SmI_2 solution bleaches to pale yellow, indicative of oxidation of Sm(II) to Sm(III). Acidification (1M HCl) and extraction to remove benzamide, followed by neutralization or basification and extraction, affords the desired chiral amine in relatively pure form.

Overall, the SmI_2 cleavage process occurs rapidly under mild conditions, leads to direct N-N bond cleavage with no loss of enantiomeric purity, and allows easy isolation and purification of the amine product. For practical purposes, however, we briefly examined less expensive reducing agents which could facilitate N-N bond cleavage. In these studies, $TiCl_3$, Zn metal, $CrCl_2$ and Pedersen's V(II) reagent ($[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$)[32] were found ineffective for the desired transformation at room temperature. Further work along these lines is in progress.

Catalytic Asymmetric Reductive Amination. Overall, we have developed a new three-step catalytic asymmetric reductive amination procedure for the convenient, chemoselective conversion of prochiral ketones into chiral hydrazino and amino derivatives (Figure 3). The process entails treating a ketone with benzoic acid hydrazide to provide the N-benzoylhydrazones **1**, followed by enantioselective hydrogenation with the Et-DuPHOS-Rh catalyst to afford highly enantiomerically-enriched N-benzoylhydrazines **2**. Attempts to perform a true one-step reductive amination by *in situ* generation of the hydrazone under the hydrogenation conditions were unsuccessful. In certain cases, the N-benzoylhydrazines **2** subsequently could be hydrolyzed directly to the corresponding hydrazines **7**. Alternatively, conversion to the desired amines was accomplished through treatment with samarium(II) iodide, thus completing the reductive amination procedure.

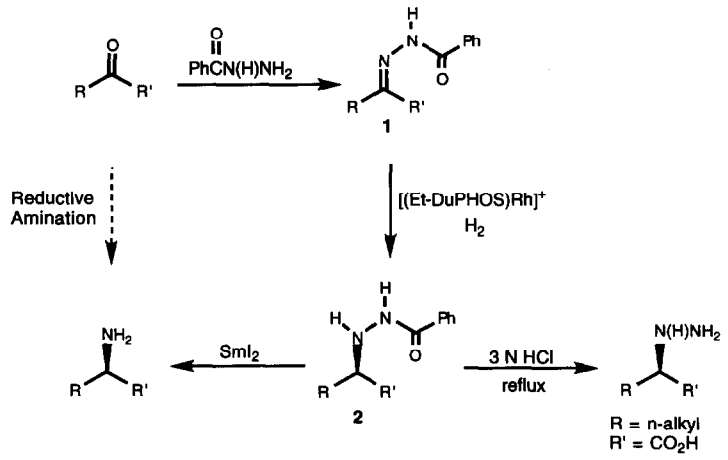
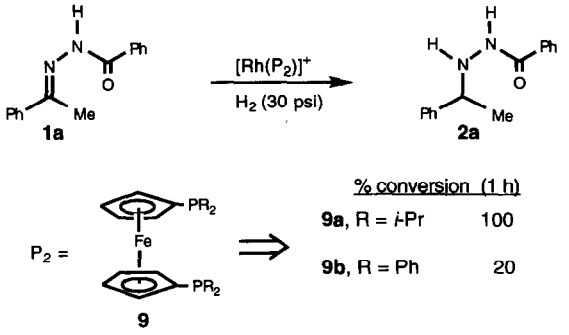


Figure 3. Catalytic Asymmetric Reductive Amination Procedure.

Catalytic Efficiency. Relative to most known asymmetric catalytic imine hydrogenations which often require high pressures, long reaction times and/or high catalyst loadings,[3] our hydrazone reductions proceeded smoothly under very mild conditions and at S/C ratios ≥1000. It was of interest to determine the nature of our enhanced catalytic efficiency relative to other systems. One possible explanation was that the electron-rich nature of the DuPHOS ligands may be partly responsible for the higher rates. To test this, we compared the efficiency of cationic Rh catalysts bearing the 1,1'-diphosphinoferrocene ligands **9a** (R = *i*-Pr) and **9b** (R = Ph) in the hydrogenation (MeOH, 30 psi H_2, 25°C, S/C = 1000) of N-benzoylhydrazone **1a** (Scheme 8).



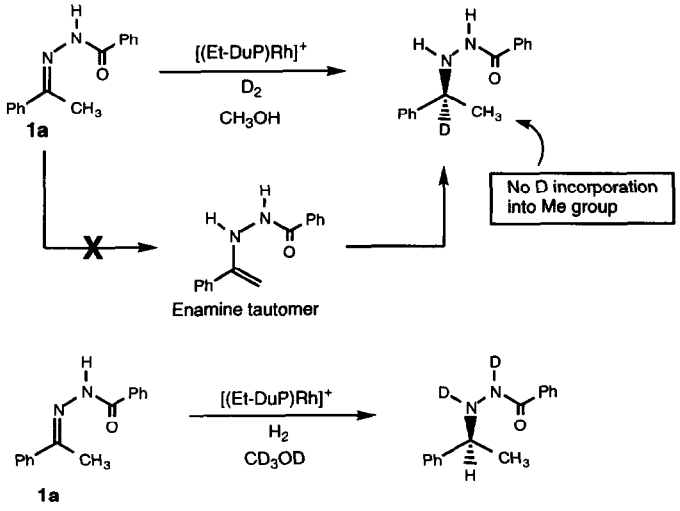
Scheme 8. Catalytic efficiency in N-acylhydrazone hydrogenations

Indeed, the catalyst bearing the electron-rich 1,1'-bis(diisopropylphosphino)ferrocene[33] (**9a**) was found to hydrogenate **1a** rapidly and quantitatively over 1 h. In contrast, only 20% conversion to product was observed over the same time period using a catalyst containing 1,1'-bis(diphenylphosphino)ferrocene (**9b**). The same trend in relative rates also was observed upon

comparing catalysts bearing the ligands 1,2-bis(diisopropylphosphino)ethane and 1,2-bis(diphenylphosphino)ethane. Based on these results, it is fairly evident that ligand electronics play some role in determining the rate of N-benzoylhydrazone hydrogenations.

A more important factor responsible for the high rates observed in the hydrogenation of **1a** is the presence of a secondary donor carbonyl oxygen atom which allows for chelation of the substrate to the rhodium center of the catalyst. As previously mentioned, substrate chelation has been shown to lead to enhanced rates in olefin hydrogenations.[6-9] Consistent with this idea, we have found that substrates which lack the carbonyl group are not hydrogenated under the mild conditions used for hydrazone **1a**. For example, neither the N-phenylimine nor the N-phenylhydrazone of acetophenone were reduced with the Et-DuPHOS-Rh catalyst over 24 h. These results further indicate the importance of the N-acyl group of **1** for the success of these reactions.

Deuterium Incorporation Studies. We have examined reduction of N-benzoylhydrazones **1** with deuterium gas in both deuterio and protio solvents in order to establish the mode of $H_2(D_2)$ addition. For example, reduction of **1a** was performed using the Et-DuPHOS-Rh catalyst and D_2 gas in CH_3OH (Scheme 9). In this experiment, deuterium was detected (^1H, ^2H, ^{13}C NMR, GC/MS) exclusively at the methine carbon with no deuterium incorporation into the methyl group. This result effectively rules out the possibility that the hydrogenation proceeds through an enamine tautomer. That is, the addition of hydrogen occurs across the C=N double bond of the N-benzoylhydrazones, not across the C=C of an enamine. The deuterium which initially resides on N is rapidly exchanged in the protic solvent CH_3OH. The N-D bond is retained in aprotic solvents such as THF.

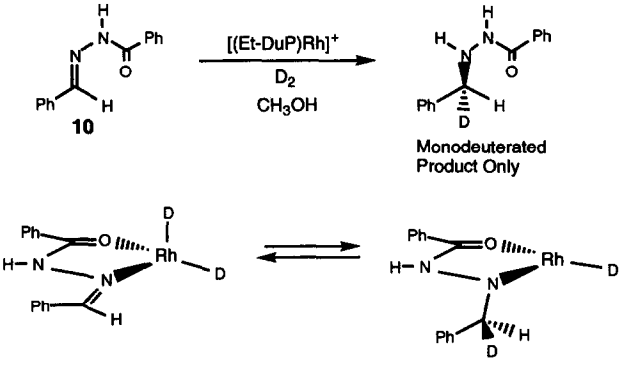


Scheme 9. Deuteration studies showing mode of reduction of N-benzoylhydrazones **1**

We also have deuterated the N-benzoylhydrazone derived from ethyl pyruvate, a substrate that should be more prone to tautomerization. Identical results were obtained; again, no deuterium incorporation into the methyl group was detected.

As a correlary experiment, we performed the reduction of **1a** under hydrogen gas in methanol-d_4 (Scheme 9). No deuterium incorporation into the carbon skeleton was observed. Together, these results indicate that the protic solvent is not involved in M-C bond cleavage during the reaction, and suggest that no H/D exchange is occuring between the M-H positions and the solvent on the timescale of the reduction.

In order to obtain further mechanistic information about the insertion process, we investigated deuteration of the N-benzoylhydrazone derived from benzaldehyde **10** (Scheme 10). This experiment was designed to provide information regarding the reversibility of insertion of the C=N moiety into the Rh-H(D) bond; any dideuterated product would indicate the occurance of rapid reversible insertion. Upon deuteration of **10** using the Et-DuPHOS-Rh catalyst, only monodeuterated product was observed, suggesting that the insertion of the C=N moiety into the Rh-D bond is irreversible.



Scheme 10. Deuteration of benzaldehyde hydrazone **10** to examine reversibility of insertion

As is so often the case, however, this result does not provide conclusive evidence favoring irreversible insertion. An alternative explanation could be that reversible insertion/β-elimination is in fact occuring, but doing so in a completely stereospecific manner. Evidence against this argument was obtained through deuteration of **10** using an analogous achiral diphosphine-Rh catalyst where stereospecific insertion/elimination would likely not be an issue. Again, only monodeuterated product was observed.

A final explanation for monodeuteration could be that insertion occurs initially to provide not a Rh-N bond and C-D bond as expected, but rather a N-D bond and Rh-C bond. Reversibility here would not be detected since susequent C-D reductive elimination has been shown to be irreversible in this system. Arguments against this mechanism would be based on the required

formation of a hindered secondary M-C bond (rather than an unhindered M-N bond) and the intermediacy of a more strained six-membered ring rather than the favored five-membered chelate formed upon initial insertion into the Rh-H bond. Both of these points speak only weakly against this pathway. On the other hand, to our knowledge, no precedent currently exists for this pathway. Overall, further studies are needed to ascertain the feasibility of insertion of hydrazone or imine C=N groups into M-H to afford a M-C-N-H linkage.

N-Acylhydrazones: Geometric Isomerism and Amide Rotamers. Many compounds containing C=N double bonds exist as *syn* and *anti* geometric isomers.[34] For example, discrete *syn* and *anti* isomers of oximes[35] and hydrazones[36] often may be detected by NMR, and in many cases may be separately isolated.[37] In the event of a high barrier to inconversion, the presence of *syn* and *anti* isomers in solution could lead to different selectivities in the asymmetric hydrogenation of the two species. In the hydrogenation of imines with Rh and Ir catalysts, some have claimed that the catalyst may accelerate the interconversion at rates faster than the hydrogenation.[3b,3g] Others, however, suggest that slow equilibrium may be responsible for lower ee's in the Ti-catalyzed asymmetric hydrogenation of acyclic imines which can exist as *syn* and *anti* isomers.[3j]

The study of N-acylhydrazones **1** are complicated by the fact that these compounds are synthesized as mixtures of *syn* and *anti* isomers and amide bond rotamers, as determined by variable temperature ^1H and ^{13}C NMR studies (CD_3CN, $CDCl_3$ and $MeOH\text{-}d_4$). Preliminary studies suggest that selectivities in our hydrogenations do appear to correlate with the ratio of the two *syn* and *anti* N-acylhydrazone isomers; hydrazones with a higher *anti*/*syn* ratios appear to be hydrogenated with higher ee's, and *visa versa*. Examination of the individual geometric isomers of substrates **1** could provide valuable information regarding the origin of enantioselection in this system. Thus far, however, we have been unable to separate the two discrete *syn* and *anti* N-acylhydrazone isomers by chromatography or fractional crystallization. A complete understanding of the influence of isomerism on enantioselectivities in N-acylhydrazone hydrogenations requires a more detailed analysis. Further studies concerning this matter, as well as other mechanistic and synthetic aspects of our reductive amination procedure, are in progress.

Experimental Section

General Procedures. All reactions and manipulations were performed in a nitrogen-filled Vacuum Atmospheres Dri-Lab glovebox or using standard Schlenk techniques. Benzene, toluene, diethyl ether (Et_2O), tetrahydrofuran (THF), glyme, hexane, and pentane were distilled from sodium-benzophenone ketyl under nitrogen. Acetonitrile (CH_3CN) and methylene chloride (CH_2Cl_2) were distilled from CaH_2. Hydrogenation reactions generally were performed with undistilled reagent grade (Baker) solvents which were deoxygenated by sparging with nitrogen for 30 min. In certain experiments, alcohol solvents were dried by distillation from Mg. The 1,2-bis(phospholano)benzene (DuPHOS) ligands were prepared as previously described.[4] The phosphines (*S*)-BINAP, (*S,S*)-BDPP, and (*S,S*)-CHIRAPHOS were purchased from Strem Chemicals (7 Mulliken Way, Newburyport, MA 01950) and used as received. Hydrogen

(99.9995%) and deuterium (99.5% min.) gas were purchased from Matheson and used as received.

Melting points were determined using a Mel-Temp apparatus in capillaries sealed under nitrogen and are uncorrected. GC analyses were performed using a Hewlett Packard Model HP 5890 GC. HPLC analyses were performed using a Hewlett Packard Model HP 1090 LC interfaced to a HP 9000 Series 300 computer workstation. Optical rotations were obtained using a Perkin Elmer Model 241 MC Polarimeter. NMR spectra were referenced relative to residual protio-solvent (ie. $CHCl_3$) peaks and were obtained on Nicolet NT-360 wide-bore (360 MHz ^1H, 146 MHz ^{31}P), Nicolet NMC-300 wide-bore (300 MHz ^1H, 120.5 MHz ^{31}P, 75.5 MHz ^{13}C) and GE QM-300 narrow-bore (300 MHz ^1H) spectrometers. ^{13}C and ^{31}P NMR chemical shifts are positive downfield (and negative upfield) from external Me_4Si and 85% H_3PO_4, respectively. IR spectra were recorded on a Nicolet 5DXB FT-IR spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY, or Pascher Mikroanalytisches Labor, Remagen-Bandorf (FRG).

N-Acylhydrazones. N-acylhydrazones were prepared by standard procedures[10] involving treatment of a carboxylic acid hydrazide (commercially available from either Aldrich Chemical Co., P.O. Box 355, Milwaukee, WI 53021 or Lancaster Synthesis Inc., P.O. Box 1000, Windham, NH 03087-9977) in tetrahydrofuran solvent with a ketone in the presence of a catalytic amount of acid catalyst (3 drops concentrated HCl). In general, most products precipitated as colorless solids from the reaction solution. The solids were filtered, washed with tetrahydrofuran, diethyl ether, and pentane, and dried in vacuo. In cases were the product did not precipitate, the reaction was monitored by thin layer chromatography. Upon completion, the reaction was concentrated, and purified by crystallization or column chromatography on silica.

Example: Acetophenone N-Benzoylhydrazone (1a). To a solution of benzoic acid hydrazide (5.70 g, 0.042 mol) in tetrahydrofuran (75 mL) was added acetophenone (5.5 g, 0.046 mol) followed by concentrated HCl (3 drops). The reaction was allowed to stir for 12 h at 25°C during which time the product precipitated as a colorless crystalline solid. The product was filtered, washed with tetrahydrofuran (1 x 30 mL), diethyl ether (3 x 60 mL) and pentane (2 x 60 mL), and the colorless crystalline product was dried in vacuo (6.65 g, 64%). NMR studies indicated the product was ca. 5:1 mixture of isomers which we presently assume are the *anti* and *syn* geometric isomers, respectively. Isomer 1 (*anti*): ^1H NMR (25°C, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 7.30-8.0 (m, 10H, Ph), 9.0 (br, 1H, NH); ^{13}C NMR (25°C, $CDCl_3$): δ 25.01 (CH_3), 126-134 (Ph). Isomer 2 (*syn*): ^1H NMR (25°C, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.30-8.0 (m, 10H, Ph), 9.0 (br, 1H, NH); ^{13}C NMR (25°C, $CDCl_3$): δ 26.54 (CH_3), 126-134 (Ph).

Example: Diethyl benzoylphosphonate N-benzoylhydrazone. Diethyl benzoylphosphonate[38] (2.37 g, 10.5 mmol) and benzoic acid hydrazide (1.36 g, 10 mmol) were dissolved in THF (10 mL). Concentrated HCl (3 drops) was added and the mixture stirred at 25°C for 24 h. Solid sodium bicarbonate was added and stirring continued for 0.5 h. The reaction mixture was filtered and the filtrate concentrated to an oil. Flash chromatography (Silica gel 60; 9/1 hexane/EtOAc) afforded the desired product as a colorless oil (2.18 g, 58%). NMR spectra indicated the presence of only a single geometric isomer. ^1H NMR ($CDCl_3$) δ 1.30 (t, J_{HH} = 7.5 Hz, 6H, CH_3), 4.1-4.3 (m, J_{HH} = 7.5 Hz, 4H, CH_2), 7.40 (m, 2H, Ph), 7.45-7.60 (m, 4H, Ph), 7.89 (br s, 2H, Ph), 8.03 (d, J_{HH} = 7.5 Hz, 2H, Ph), 13.8 (br s, 1H, NH); IR (KBr) ν (cm^{-1}) 1700 s, 1540 m, 1268 vs, 1014 vs, 698 s; HRMS *m/z* 361.1318 ($(M+H)^+$, exact mass calcd for $C_{18}H_{22}N_2O_4$ 361.1317).

Asymmetric Hydrogenation of N-Acylhydrazones (1): General Procedure. In a nitrogen-filled dry box, a 100 mL Fisher-Porter tube was charged with a stir bar and substrate (0.5 to 1.26 mmol), followed by degassed solvent (10 to 20 mL, ca. 0.05 to 0.10 M in substrate), and catalyst (0.1-0.2 mol %). After six vacuum/H_2 cycles to purge the lines of air and two vacuum/H_2 cycles on the

reaction mixture, the tube was pressurized to an initial pressure of 15 to 60 psig H_2 (Matheson, 99.998%). The reactions were allowed to stir at temperatures ranging from -15°C to 50°C until no further hydrogen uptake was observed. Complete (100%) conversion to product was indicated by GC, TLC and ^1H NMR analyses, unless otherwise noted. The reactions were concentrated, and the residue passed through a short SiO_2 column (EtOAC/hexane or Et_2O/pentane, 50/50) to remove catalyst residues. Without further purification, the enantiomeric excesses were determined directly with the crude products thus obtained.

Example: (*S*)-(-)-1-Phenyl-1-(2-benzoylhydrazino)ethane (2a). A 100 mL Fisher-Porter tube was charged with a stir bar, acetophenone N-benzoyhydrazone (200 mg, 0.8 mmol), 2-propanol (10 mL) and rhodium catalyst [(COD)Rh(1,2-Bis((2*R*,5*R*)-2,5-diethylphospholano)-benzene)]$^+CF_3SO_3^-$ (1.0 mg, 0.00136 mmol). While the substrate was not completely soluble in 2-propanol under these conditions, the reaction proceeded normally. The tube was then connected to a hydrogen tank (Matheson, 99.998%) and the lines were purged of air by six vacuum/H_2 cycles. After two vacuum/H_2 cycles on the reaction mixture, the tube was pressurized to an initial pressure of 60 psig H_2 and the reaction tube was rapidly placed in a 0°C bath. After allowing 20 min. for equilibration, the stirring was started and the reaction was allowed to proceed until no further hydrogen uptake was observed (12 h). At this point, the reaction was homogeneous. Complete conversion to product was indicated by thin layer chromatography and capillary gas chromatography (methyl silicone column). The reaction was concentrated on a rotovap and the residue was chromatographed on a short SiO_2 column (ca. 6 x 0.5 cm) using 50% ethyl acetate/hexane as eluent. Fractions containing product were concentrated on a rotovap to give (*S*)-(-)-1-phenyl-1-(2-benzoylhydrazino)ethane (**2a**) as a colorless crystalline solid (182 mg, 91%). Enantiomeric excess analysis by HPLC using the Daicel column Chiralcel OJ (90/10 hexane/2-propanol; 40°C, 0.5 mL/min flow) indicated product of 92% enantiomeric excess. mpt 75-76.5°C; $[\alpha]_D^{20}$ = -163.6° (*c* 2.72, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.50 (d, J_{HH} = 6.7 Hz, 3H, CH_3), 4.37 (q, J_{HH} = 6.7 Hz, 1H, NCH), 7.2-7.6 (m, 8H, Ph), 7.7 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.16 (CH_3), 60.29 (NCH), 127.07, 127.41, 127.78, 128.72, 131.91, 132.98, 142.94, 167.42 (C=O); HRMS (EI, direct insert) *m/z* 240.1259 (M^+, exact mass calcd for $C_{15}H_{16}N_2O$ 240.1263); Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.81; H, 6.83; N, 11.61.

The same reaction using the antipodal catalyst, [(COD)Rh(1,2-Bis((2*S*,5*S*)-2,5-diethylphospholano)benzene)]$^+CF_3SO_3^-$, afforded the opposite enantiomer of the product, (*R*)-(+)-1-phenyl-1-(2-benzoylhydrazino)ethane, with identical enantiomeric excess (92% ee).

Chemoselectivity - Competition Experiments. Hydrogenation experiments aimed at establishing chemoselectivities in the hydrogenation of N-benzoylhydrazone (**1a**) versus other substrates were performed as described above for the asymmetric hydrogenation of acetophenone N-benzoylhydrazone (**1a**) with the exception that 1 molar equivalent of the test substrate (relative to **1a**) was added to the mixture, and the reaction was conducted at 20°C under 30 psi H_2 pressure for 1 h . Complete and exclusive conversion to the N-benzoylhydrazine **2a** was indicated by GC measurements (HP-1 methyl silicone capillary column); within the limits of detection, no reduction of the following substrates was observed under these conditions: 1-methyl-1-cyclohexene, cyclohexene, α-methylstyrene, 3-phenyl-1-propene, acetophenone, benzaldehyde, acetophenone N-phenylimine, 1-bromohexane, nitrobenzene, and benzonitrile. For the substrates 1-octene, 4-octyne and diphenylacetylene, minor amounts (< 2%) of hydrogenation products (n-octane, cis-4-octene, and *cis* and *trans*-stilbene (ca. 3.5:1 ratio), respectively) were observed under these conditions. Other tolerable functional groups are present in the N-aroylhydrazones **1**. In the case of the substrate benzonitrile, complete reduction of **1a** required 3 h due to inhibition by the nitrile. Hydrogenation of aldehyde, olefin and alkyne substrates was shown to take place to varying extents in the absence of **1a**. The N-benzoylhydrazine product **2a**, however, was found to almost completely inhibit reduction of aldehyde, olefin and alkyne substrates under the conditions above.

Hydrolysis of 2-(Benzoylhydrazino) Esters: Example. To (*R*)-(+)-ethyl 2-(2-benzoylhydrazino)propionate (1.2 g, 5.08 mmol, 79% ee) was added 3 N HCl (12 mL) and the mixture refluxed for 3 h. Upon cooling, benzoic acid precipitated as a colorless crystalline solid. After filtration, the aqueous layer was extracted with Et_2O (3 x 20 mL) and then concentrated to afford the product, (*R*)-(+) α-hydrazino-propionic acid, as the hydrochloride salt (0.653 g, 91%); $[\alpha]_D^{20}$ = +17.0° (*c* 1, H_2O); ^1H NMR (DMSO-d_6) δ 1.25 (d, J_{HH} = 7.14 Hz, 3H, CH_3), 3.75 (q, J_{HH} = 7.14 Hz, 1H, CH), 7.40 (br, NH); ^{13}C NMR (D_2O) δ 15.50 (CH_3), 58.18 (CH), 175.03 (C=O); ^{15}N NMR (D_2O) δ -303.91, -313.65.

Samarium(II) Iodide-Induced N-N Bond Cleavage: General Procedure. To N-benzoylhydrazines (**2**) in methanol was added rapidly dropwise a solution of samarium(II) iodide (2.2 mole equivalents, obtained as a 0.10 M tetrahydrofuran solution from Alfa Products, P.O. Box 8247, Ward Hill, MA 01835-0747). Upon addition, the blue color of the samarium(II) iodide solution decolorized. After complete addition, the reaction was allowed to stir for 30 min. The reaction was then concentrated on a rotovap, and to the resulting residue was added 1 M HCl. The aqueous layer was extracted with diethyl ether to remove essentially all organic by-products. These combined fractions were discarded. The aqueous layer was made basic to litmus by the addition of 3 M NaOH and then was extracted with diethyl ether. The combined ether extractions was diluted 1:1 with pentane and then were dried over potassium carbonate or a small amount of magnesium sulfate. Concentration of the ether provided the amine as essentially the only product.

Example: Samarium(II) Iodide-Induced N-N Bond Cleavage of 1-Phenyl-1-(2-benzoylhydrazino)ethane. To (*S*)-(-)-1-phenyl-1-(2-benzoylhydrazino)ethane (0.40 g, 1.66 mmol, 89% ee) in methanol (7 mL) was added rapidly dropwise a solution of samarium(II) iodide (70 mL of a 0.05 M solution in tetrahydrofuran). After complete addition, the reaction was allowed to stir for 30 min. The reaction was then concentrated on a rotovap, and to the resulting residue was added 1 M HCl (15 mL). The aqueous layer was extracted with diethyl ether (8 x 25 mL). The aqueous layer was made basic to litmus by the addition of 3 M NaOH and then was extracted with diethyl ether (8 x 25 mL). The combined ether extractions diluted with pentane (1:1) and dried over a small amount of magnesium sulfate. Concentration of the ether/pentane solution on a rotovap provided the product (*S*)-(-)-α-methylbenzylamine as a colorless oil (0.144 g, 72%): $[\alpha]_D^{20}$ = -37.1° (*c* 1.33, C_6H_6), ^1H NMR ($CDCl_3$): δ 1.40 (d, J_{HH} = 6.3 Hz, 3H, CH_3), 1.70 (br, 2H, NH), 4.14 (q, J_{HH} = 6.3 Hz, 1H, CH), 7.25 (m, 1H, Ph), 7.45 (m, 4H, Ph). The enantiomeric purity of the amine product (*S*)-(-)-α-methylbenzylamine was determined to be 89% ee using chiral capillary GC methods (J & W Cyclodex B column, 80°C, isothermal, (*R*) t_1 20.57 min; (*S*) t_2 21.33 min).

Analytical and NMR Data for N-Aroylhydrazine Products 2

1-*p*-methoxyphenyl-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.43 (d, J_{HH} = 6.6 Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.24 (q, J_{HH} = 6.6 Hz, 1H, NCH), 6.85 (d, J_{HH} = 8.7 Hz, 2H, Ph), 7.20-7.55 (m, 5H, Ph), 7.67 (d, J_{HH} = 8.7 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.04 (CH_3), 55.37 (OCH_3), 59.48 (NCH), 114.04, 127.05, 128.48, 128.67, 131.82, 133.01, 134.98, 159.15 (aromatic C-O), 167.38 (C=O); HRMS (EI, direct insert) *m/z* 270.1313 (M^+, exact mass calcd for $C_{16}H_{18}N_2O_2$ 270.1369).

1-*p*-carboethoxyphenyl-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.38 (t, J_{HH} = 7.15 Hz, 3H, CH_3), 1.45 (d, J_{HH} = 6.65 Hz, 3H, CH_3), 4.35 (q, J_{HH} = 7.15 Hz, 2H, CH_2), 4.38 (q, J_{HH} = 6.65 Hz, 1H, NCH), 7.35-7.55 (m, 5H, Ph), 7.68 (d, J_{HH} = 8.6 Hz, 2H, Ph), 8.02 (d, J_{HH} = 8.6 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.54 (CH_3), 21.25 (CH_3), 60.16 (NCH), 61.11 (OCH_2), 127.09,

127.37, 128.80, 130.05, 132.09, 132.69, 148.17, 166.56 (ester C=O), 167.61 (amide C=O); HRMS (EI, direct insert) *m/z* 312.1445 (M^+, exact mass calcd for $C_{18}H_{20}N_2O_3$ 312.1474).

1-*p*-nitrophenyl-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.47 (d, J_{HH} = 6.7 Hz, 3H, CH_3), 4.46 (q, J_{HH} = 6.7 Hz, 1H, NCH), 7.35-7.65 (m, 7H, Ph), 8.08 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.44 (CH_3), 59.89 (NCH), 123.99, 127.07, 128.27, 128.88, 132.29, 132.48, 150.92 (aromatic C-N), 167.90 (C=O); Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.78; H, 5.08; N, 14.67.

1-*p*-bromophenyl-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.48 (d, J_{HH} = 6.7 Hz, 3H, CH_3), 4.36 (q, J_{HH} = 6.7 Hz, 1H, NCH), 7.25-7.55 (m, 7H, Ph), 7.67 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.23 (CH_3), 59.77 (NCH), 121.61, 127.07, 128.84, 129.20, 131.88, 132.12, 132.86, 142.06, 167.59 (C=O); Anal. Calcd for $C_{15}H_{15}BrN_2O$: C, 56.44; H, 4.74; N, 8.78. Found: C, 56.11; H, 4.63; N, 8.53.

1-phenyl-1-(2-benzoylhydrazino)propane: ^1H NMR ($CDCl_3$) δ 0.85 (t (dd), J_{HH} = 7.45 Hz, 3H, CH_3), 1.79 (m, 1H, CH_2), 1.95 (m, 1H, CH_2), 4.06 (dd, J_{HH} = 8.76, 5.42 Hz, 1H, NCH), 7.25-7.55 (m, 8H, Ph), 7.65 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 10.47 (CH_3), 28.03 (CH_2), 66.80 (NCH), 127.01, 127.59, 128.01, 128.45, 128.53, 131.67, 132.99, 141.55, 167.32 (C=O); HRMS (EI, direct insert) *m/z* 254.1419 (M^+, exact mass calcd for $C_{16}H_{18}N_2O$ 254.1419).

1,2-diphenyl-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 3.13 (m, 2H, CH_2), 4.06 (dd, J_{HH} = 7.3 Hz, 1H, NCH), 7.15-7.80 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$) δ 42.26 (CH_2), 65.75 (NCH), 126.19, 126.70, 126.95, 127.41, 127.60, 128.16, 128.61, 128.77, 129.02, 131.34, 132.61, 137.70, 141.00, 166.93 (C=O); HRMS (EI, direct insert) *m/z* 316.1544 (M^+, exact mass calcd for $C_{21}H_{20}N_2O$ 316.1576).

1-(2-naphthyl)-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) d 1.52 (d, J_{HH} = 6.62 Hz, 3H, CH_3), 4.45 (q, J_{HH} = 6.62 Hz, 1H, NCH), 7.3-7.9 (m, 7H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.26 (CH_3), 60.36 (NCH), 125.30, 125.94, 126.21, 126.30, 127.04, 127.79, 127.99, 128.50, 128.67, 131.86, 132.85, 133.17, 133.53, 140.51, 167.50 (amide C=O); HRMS (EI, direct insert) *m/z* 290.1405 (M^+, exact mass calcd for $C_{19}H_{18}N_2O$ 290.1419).

ethyl 2-(2-benzoylhydrazino)propionate: ^1H NMR ($CDCl_3$) δ 1.26 (t, J_{HH} = 7.15 Hz, 3H, CH_3), 1.40 (d, J_{HH} = 7.04 Hz, 3H, CH_3), 3.87 (q, J_{HH} = 7.04 Hz, 1H, NCH), 4.18 (m, 2H, OCH_2), 7.40-7.60 (m, 3H, Ph), 7.72 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.02 (CH_3), 15.92 (CH_3), 58.30 (OCH_2), 60.97 (NCH), 126.94, 128.42, 131.71, 132.45, 166.99 (amide C=O), 173.38 (ester C=O); HRMS (EI, direct insert) *m/z* 236.1132 (M^+, exact mass calcd for $C_{12}H_{16}N_2O_3$ 236.1161).

methyl 2-(2-benzoylhydrazino)butyrate: ^1H NMR ($CDCl_3$) δ 1.04 (t, J_{HH} = 7.45 Hz, 3H, CH_3), 1.90 (overlapping dq, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.94 (dd, J_{HH} = 6.12 Hz, 1H, NCH), 7.40-7.80 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 10.21 (CH_3), 24.04 (CH_2), 52.22 (OCH_3), 64.59 (NCH), 127.17, 128.76, 132.07, 132.61, 167.20 (amide C=O), 173.65 (ester C=O); HRMS (EI, direct insert) *m/z* 236.1139 (M^+, exact mass calcd for $C_{12}H_{16}N_2O_3$ 236.1161).

methyl 2-(2-benzoylhydrazino)valerate: ^1H NMR ($CDCl_3$) δ 0.93 (t, J_{HH} = 7.35 Hz, 3H, CH_3), 1.42 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.77 (dd, J_{HH} = 6.20 Hz, 1H, NCH), 7.35-7.70 (m, 3H, Ph), 7.70-7.80 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.78 (CH_3), 18.92 (CH_2), 32.71 (CH_2), 51.90 (OCH_3), 63.08 (NCH), 126.94, 128.45, 131.74, 132.48, 166.96 (amide C=O),

173.72 (ester C=O); HRMS (EI, direct insert) *m/z* 250.1319 (M^+, exact mass calcd for $C_{13}H_{18}N_2O_3$ 250.1318).

methyl 2-phenyl-2-(2-benzoylhydrazino)acetate: ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H, OCH_3), 5.01 (s, 1H, NCH), 7.35-7.8 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 52.55 (OCH_3), 67.23 (NCH), 127.24, 128.58, 128.74, 128.95, 129.00, 132.10, 132.56, 135.26, 167.53 (amide C=O), 171.95 (ester C=O); Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.52; H, 5.63; N, 9.83.

3-methyl-2-(2-*p*-dimethylaminobenzoylhydrazino)butane: ^1H NMR ($CDCl_3$) δ 0.98 (d, J_{HH} = 6.15 Hz, 3H, CH_3), 1.10 (d, J_{HH} = 6.73 Hz, 3H, CH_3), 1.21 (d, J_{HH} = 6.70 Hz, 3H, CH_3), 2.12 (m, 1H, CH), 3.03 (s, 6H, NCH_3), 3.34 (dq, J_{HH} = 6.63, 4.89 Hz, 1H, NCH), 6.62 (d, J_{HH} = 8.75 Hz, 2H, Ph), 7.84 (d, J_{HH} = 8.75 Hz, 2H, Ph).

1-phenyl-1-(2-*p*-methoxybenzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.48 (d, J_{HH} = 6.6 Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.27 (q, J_{HH} = 6.6 Hz, 1H, NCH), 6.88 (d, J_{HH} = 8.7 Hz, 2H, Ph), 7.20-7.55 (m, 5H, Ph), 7.69 (d, J_{HH} = 8.7 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.09 (CH_3), 55.46 (OCH_3), 60.13 (NCH), 113.89, 125.22, 127.38, 127.61, 128.60, 128.86, 143.13, 162.46 (aromatic C-O), 167.42 (C=O); HRMS (EI, direct insert) *m/z* 270.1330 (M^+, exact mass calcd for $C_{16}H_{18}N_2O_2$ 270.1369).

1-phenyl-1-(2-*p*-dimethylaminobenzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.50 (d, J_{HH} = 6.7 Hz, 3H, CH_3), 3.00 (s, 3H, NCH_3), 4.34 (q, J_{HH} = 6.7 Hz, 1H, NCH), 6.65 (d, J_{HH} = 8.85 Hz, 2H, Ph), 7.20-7.55 (m, 5H, Ph), 7.64 (d, J_{HH} = 8.85 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.82 (CH_3), 39.89 (NCH_3), 59.91 (NCH), 110.93, 119.43, 127.18, 127.23, 128.24, 128.30, 143.15, 152.47 (aromatic C-N), 167.31 (C=O); HRMS (EI, direct insert) *m/z* 283.1653 (M^+, exact mass calcd for $C_{17}H_{21}N_3O$ 283.1684).

1-cyclohexyl-1-(2-benzoylhydrazino)ethane: ^1H NMR ($CDCl_3$) δ 1.06 (d, J_{HH} = 6.52 Hz, 3H, CH_3), 1.00-1.35 (m, 5H, CH_2), 1.45 (m, 1H, CH), 1.60-1.85 (m, 5H, CH_2), 2.93 (d, J_{HH} = 6.52, 4.95 Hz, 1H, NCH), 7.40-7.60 (m, 3H, Ph), 7.80 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.34 (CH_3), 26.60, 26.73, 26.85, 28.11, 30.04, 41.69, 60.81 (NCH), 127.11, 128.78, 131.90, 133.13, 167.44 (C=O); HRMS (EI, direct insert) *m/z* 246.1722 (M^+, exact mass calcd for $C_{15}H_{22}N_2O$ 246.1732).

Enantiomeric Excess Determinations for N-acylhydrazines (2):

Enantiomeric excesses listed are the average value obtained from 2-3 experiments. Enantiomeric excesses were determined as follows: **1-phenyl-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: (*R*) t_1 15.6 min; (*S*) t_2 18.5 min); **1-*p*-methoxyphenyl-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.75 mL/min, 10% 2-propanol/ 90% hexane: (*R*) t_1 17.47 min; (*S*) t_2 22.64 min); **1-*p*-carboethoxyphenyl-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: (*S*) t_1 33.08 ; (*R*) t_2 37.39 min); **1-*p*-nitrophenyl-1-(2-benzoylhydrazino)-ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.75 mL/min, 10% 2-propanol/ 90% hexane: (*S*) t_1 41.38 min; (*R*) t_2 48.55 min); **1-*p*-bromophenyl-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OB, 40°C, 1.0 mL/min, 5% 2-propanol/ 95% hexane: (*R*) t_1 12.75 min; (*S*) t_2 20.55 min); **1-phenyl-1-(2-benzoylhydrazino)propane** (HPLC, Daicel Chiralcel OB, 40°C, 0.5 mL/min, 5% 2-propanol/ 95% hexane: (*R*) t_1 15.26 min; (*S*) t_2 18.87 min); **1,2-diphenyl-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: (*S*) t_1 22.36 min; (*R*) t_2 25.09 min); **1-(2-naphthyl)-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 1.0 mL/min, 10% 2-propanol/ 90%

hexane: (*R*) t_1 17.63 min; (*S*) t_2 21.08 min); **ethyl 2-(2-benzoylhydrazino)propionate** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: (*R*) t_1 13.55 min; (*S*) t_2 15.16 min); **methyl 2-(2-benzoylhydrazino)propionate** (HPLC, Daicel Chiralcel OJ, 40°C, 1.0 mL/min, 5% 2-propanol/ 95% hexane: t_1 18.23 min; t_2 20.95 min); **methyl 2-(2-benzoylhydrazino)butyrate** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: (*R*) t_1 15.87 min; (*S*) t_2 17.22 min); **methyl 2-phenyl-2-(2-benzoylhydrazino)acetate** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: t_1 27.35 min; t_2 33.05 min); **3-methyl-2-(2-benzoylhydrazino)butane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 5% 2-propanol/ 90% hexane: t_1 14.34 min; t_2 15.99 min); **1-phenyl-1-(2-*p*-nitrobenzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 1.0 mL/min, 10% 2-propanol/ 90% hexane: (*S*) t_1 20.01 min; (*R*) t_2 23.84 min); **1-phenyl-1-(2-*p*-methoxybenzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: (*S*) t_1 25.46 min; (*R*) t_2 27.77 min); **1-phenyl-1-(2-*p*-dimethylaminobenzoyl-hydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 7.5% 2-propanol/ 92.5% hexane: (*R*) t_1 46.70 min; (*S*) t_2 48.97 min); **3-methyl-2-(2-*p*-dimethylaminobenzoylhydrazino)butane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 10% 2-propanol/ 90% hexane: t_1 16.61 min; t_2 18.47 min); **2-phenyl-2-(acetylhydrazino)ethane** (GC, Chrompack, XE60-(*S*)-Val, 175°C (isothermal) (*S*) t_1 30.36 min; (*R*) t_2 31.57 min); **1-cyclohexyl-1-(2-benzoylhydrazino)ethane** (HPLC, Daicel Chiralcel OJ, 40°C, 0.5 mL/min, 5% 2-propanol/ 95% hexane: (*R*) t_1 12.60 min; (*S*) t_2 13.41 min);

Optical Rotations of N-aroylhydrazines (2):

(*S*)-1-phenyl-1-(2-benzoylhydrazino)ethane (92% ee; $[\alpha]_D^{20}$ = -163.6° (*c* 2.72, $CHCl_3$)); **(*S*)-1-*p*-methoxyphenyl-1-(2-benzoylhydrazino)ethane** (88% ee; $[\alpha]_D^{20}$ = -188.9° (*c* 0.67, $CHCl_3$)); **(*S*)-1-*p*-carboethoxyphenyl-1-(2-benzoylhydrazino)ethane** (96% ee; $[\alpha]_D^{20}$ = -200.0° (*c* 1, $CHCl_3$)); **(*S*)-1-*p*-bromophenyl-1-(2-benzoyl-hydrazino)ethane** (98% ee; $[\alpha]_D^{20}$ = -191.6° (*c* 1, $CHCl_3$)); **(*S*)-1-*p*-nitrophenyl-1-(2-benzoylhydrazino)ethane** (97% ee; $[\alpha]_D^{20}$ = -211.8° (*c* 1, $CHCl_3$)); **(*S*)-1-(2-naphthyl)-1-(2-benzoylhydrazino)ethane** (95% ee; $[\alpha]_D^{20}$ = -204.5° (*c* 3.90, $CHCl_3$)); **methyl 2-phenyl-2-(2-benzoylhydrazino)acetate** (96% ee; $[\alpha]_D^{20}$ = -98.0° (*c* 1, $CHCl_3$)); **(*S*)-ethyl 2-(2-benzoylhydrazino)propionate** (88% ee; $[\alpha]_D^{20}$ = -57.4° (*c* 1, $CHCl_3$)); **(*S*)-methyl 2-(2-benzoylhydrazino)butyrate** (91% ee; $[\alpha]_D^{20}$ = -65.0° (*c* 1, $CHCl_3$)); **(*S*)-1-phenyl-1-(2-*p*-methoxybenzoylhydrazino)ethane** (96% ee; $[\alpha]_D^{20}$ = -163.6° (*c* 1, $CHCl_3$)); **(*S*)-1-phenyl-1-(2-*p*-dimethylaminobenzoylhydrazino)ethane** (92% ee; $[\alpha]_D^{20}$ = -150.4° (*c* 1, $CHCl_3$)); **(*S*)-1-phenyl-1-(2-benzoylhydrazino)propane** (84% ee; $[\alpha]_D^{20}$ = -132.2° (*c* 1, $CHCl_3$)); **(*S*)-1,2-diphenyl-1-(2-benzoylhydrazino)ethane** (84% ee; $[\alpha]_D^{20}$ = -79.8° (*c* 1, $CHCl_3$)); **(*S*)-1-cyclohexyl-1-(2-benzoylhydrazino)ethane** (72% ee; $[\alpha]_D^{20}$ = +0.6° (*c* 1, $CHCl_3$); **3-methyl-2-(2-benzoylhydrazino)butane** (60% ee; $[\alpha]_D^{20}$ = +6.8° (*c* 1, $CHCl_3$)); **3-methyl-2-(2-*p*-dimethylamino-benzoylhydrazino)butane** (73% ee; $[\alpha]_D^{20}$ = +12.4° (*c* 1, $CHCl_3$)).

Absolute Configurations. Absolute configurations for N-aroylhydrazone reduction products were established by converting the N-aroylhydrazines (**2**) to the corresponding primary amine via the samarium(II) iodide-induced N-N bond cleavage, followed by comparison of the sign of optical rotation of the amine with that of the authentic configurationally assigned compound. The following referenced compounds were used for comparison: (*S*)-(-)-α-methylbenzylamine[39] ($[\alpha]_D^{20}$ = -40.3° (*c* 1.33, C_6H_6, commercial sample)); (*R*)-(+)-α-(2-naphthyl)ethylamine[39] ($[\alpha]_D^{20}$ =

+21.0° (*c* 2.0, ethanol)); (*S*)-(-)-α-ethylbenzylamine[39,40] ($[\alpha]_D^{20}$ = -21.7° (*c* 1.0, benzene)); (*R*)-(+)-α-(*p*-methoxyphenyl)ethylamine[41] ($[\alpha]_D^{20}$ = +21.6° (neat)); (*R*)-(-)-1,2-diphenylethylamine[39,42] ($[\alpha]_D^{19}$ = -51.2° (*c* 3.7, ethanol)); (*R*)-(+)-α-(p-nitrophenyl)ethylamine[43] ($[\alpha]_D^{20}$ = +16.7° (neat)); (*S*)-(+)-α-cyclohexyl-ethylamine[44] ($[\alpha]_D^{20}$ = +3.6° (*c* 1, $CHCl_3$, commercial sample)); (*S*)-α-hydrazinopropionic acid[45] ($[\alpha]_D^{20}$ = -28.5° (*c* 1, 6 N HCl)).

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* Address correspondence to this author at Duke University, Department of Chemistry, P.M. Gross Chemical Laboratory, Durham, NC 27706.

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