Asymmetric Hydrogenation

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Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Hydrazones and Other Ketimines**

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Abstract: *We report the use of nickel catalysts for the catalytic transfer hydrogenation of hydrazones and other ketimines with formic acid. Strongly donating bisphosphines must be used to support the catalysts. As in enzymatic catalysis, attractive weak interactions may be important for stereochemical control by the nickel/binapine catalyst.*

Chiral alkyl amines are common in drugs and agrochemicals. They are present in about 20% of blockbuster drugs. In the past, classical resolution was often used to prepare chiral alkyl amines.[1] In recent decades, metal-catalyzed hydrogenation reactions of imines, enamines, and enamides have emerged as economic alternatives for the large-scale preparation of pharmaceuticals.[2] Today, noble-metal catalysts based on Rh,[3] Ir,[4] and Ru[5] dominate the field of asymmetric (transfer) hydrogenation, with the recent addition of Pd catalysts.[6] In particular, millions of turnovers are possible with iridium hydrogenation catalysts, and they are used in the industrial production of the cough suppressant dextromethorphan[7] and the herbicide metolachlor.[8] However, these heavy metals are extremely expensive and highly toxic and pollute our ecosystems if released. Furthermore, their reserves in the Earth's crusts are very limited; they are produced in dozens of tons yearly.

First-row metals are much cheaper and less toxic or nontoxic. Every year, they are produced in millions of tons. Back in 1996, Mukaiyama and co-workers disclosed a cobalt-catalyzed asymmetric reduction with a modified borohydride, but the imines were limited to *N*-phosphinyl ketimines.[9] At a similar time, Buchwald and co-workers successfully applied chiral titanocene catalysts to the hydrogenation and hydrosilylation of aryl ketimines.[10] Lipshutz and Shimizu also reported a copper-catalyzed asymmetric hydrosilylation of aryl ketimines.[11] In recent years, there has been renewed interest in finding new first-row-metal catalysts. For example, the research groups of Beller[12] and Morris[13] independently developed iron catalysts for the asymmetric hydrogenation of imines, but only *N*-phosphinyl ketimines were hydrogenated with high enantioselectivity. In another line of research, chiral phosphoric acids were successfully used as transition-metal-free catalysts for asymmetric ketimine reduction.[14]

Nickel is much cheaper than the noble metals. Recent prices of nickel, iridium, and rhodium were around $16, $16000, and $40000 per kg, respectively.[15] The production of nickel is as high as 2.1 million tons a year, as compared with 30 tons for rhodium. Discrete nickel complexes of N-heterocyclic carbenes and phosphines have been examined in nonstereoselective hydrogenation and hydrosilylation reactions of C=C,[16] C=O,[17] and C=N bonds.[18] Furthermore, the nickel-catalyzed asymmetric hydrogenation of α-amino-β-ketoesters under dynamic kinetic resolution has been reported[19] as well as the hydrosilylation of some ketones (around 80% *ee*).[20] We recently disclosed a nickel/binapine catalyst for the asymmetric transfer hydrogenation of enamides.[21] Heterogeneous nickel catalysts modified with tartaric acid derivatives have been applied in the asymmetric hydrogenation of ketones (Orito reaction), although the success of this approach has been quite limited.[22]

Herein, we describe the use of nickel catalysts for the asymmetric transfer hydrogenation of hydrazones and other ketimines.[23] Recently, Zhang and co-workers reported an asymmetric reductive amination via hydrazone intermediates with an Ir/*f*-binaphane catalyst.[24] The hydrazine products can be reduced to release free alkyl amines by treatment with SmI_2[23] and hydrogenation over nickel.[25]

In our study of the nickel-catalyzed transfer hydrogenation of a model hydrazone of acetophenone, highly electron rich, bulky bisphosphines showed high activity (Scheme 1). In particular, (*S*)-binapine, which was invented by Zhang and co-workers, afforded the product with 97% *ee* and full conversion.[26] The related bisphosphines BenzP* and QuinoxP* also afforded good selectivity,[3f,27] and with *i*Pr-DuPhos the product was obtained with 80% *ee*.[28] Notably, one of the josiphos ligands of Togni and co-workers gave almost perfect stereoselectivity.[29] The less donating bisphosphine ligands binap, segphos, and dipamp, with two or three aryl rings attached to each phosphorus center, were completely inactive in nickel catalysis. Iron, cobalt, and copper salts were also tested, but no active catalyst was found with binapine.

A 2:2 molar mixture of HCO_2H and Et_3N was used as a hydrogen surrogate. Sometimes partial hydrolysis of the hydrazone was detected and dry molecular sieves were included to prevent the unwanted side reaction.[30] In alcoholic solvents (Table 1, entries 1–5), the reaction was much faster than in aprotic solvents (entries 7–10).[31]

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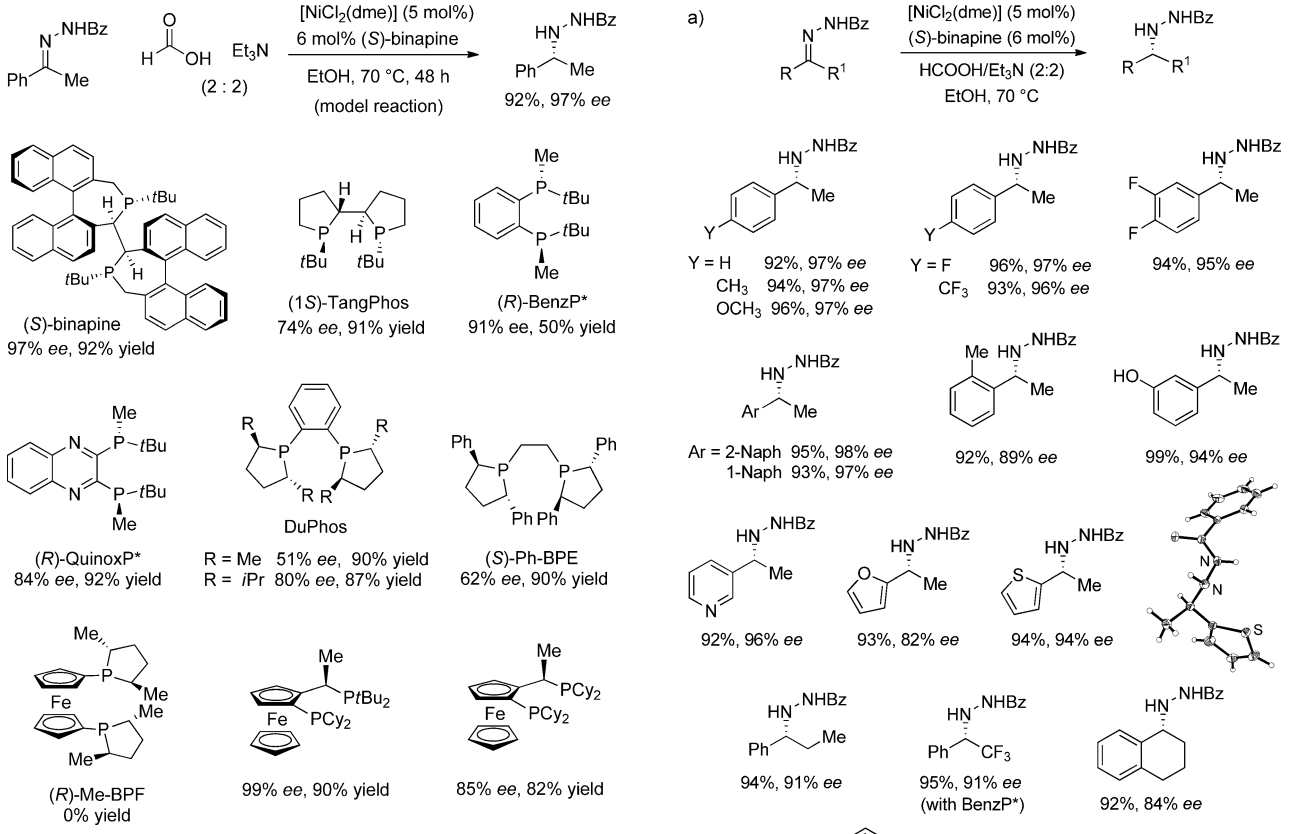
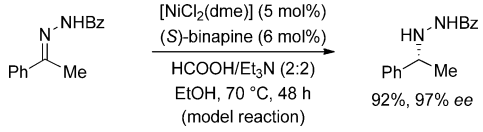


Scheme 1. Performance of chiral bisphosphines in a model reaction of an aryl hydrazone. The reactions were carried out on a 0.1 mmol scale, and the yields were determined by GC. Bz = benzoyl, Cy = cyclohexyl, dme = dimethoxyethane.

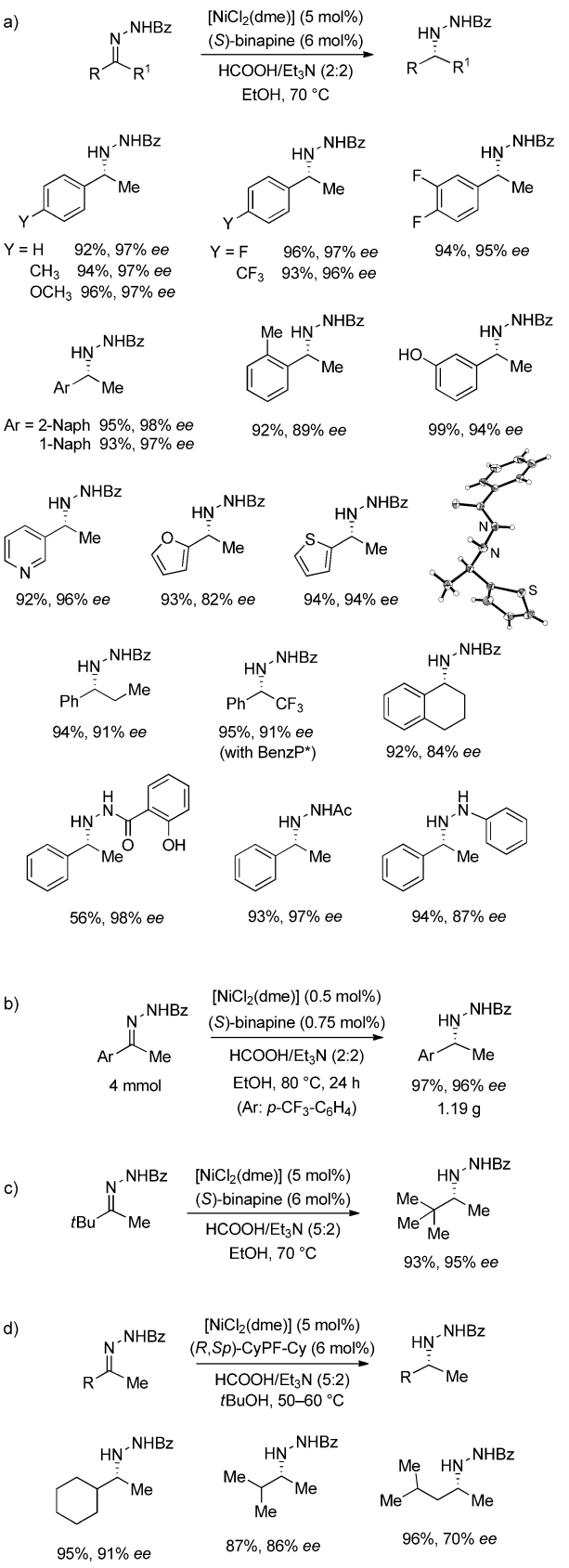
Table 1: Effect of solvents in the model transfer hydrogenation.[a]



Entry	Solvent[b]	Conversion [%]	Yield [%][c]	*ee* [%]
1	MeOH	94	92	96
2	EtOH	96	95	97
3	*i*PrOH	94	93	97
4	*t*BuOH	95	95	97
5	DMSO	82	82	96
6	DMF	92	92	89
7	THF	17	17	96
8	dioxane	15	14	94
9	toluene	25	23	95
10	$PhCF_3$	35	34	97

[a] Reactions were carried out on a 0.1 mmol scale. [b] DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide. [c] The yield was determined by GC.

The scope of the reaction of arylated hydrazones was quite broad (Scheme 2a). Both electron-rich and electron-poor aryl groups and some heteroaryl rings can be present. One hydrazine product containing a thiophene ring was used to grow single crystals (vapor diffusion of pentane into



Scheme 2. Nickel-catalyzed asymmetric transfer hydrogenation of a variety of hydrazones. The yield given in each case is for the isolated product of a reaction carried out on a 0.5 mmol scale, unless stated otherwise.[37]

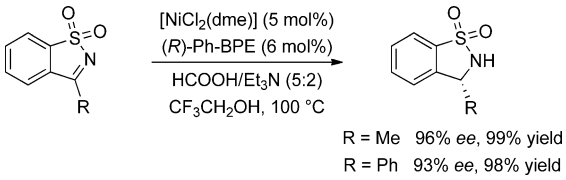
a solution in ethyl acetate). X-ray diffraction analysis established a 1*R* absolute configuration. This result for the first time conclusively affirmed assignments made in previous studies on the basis of chemical derivatization and the sign of optical rotation.

The *N*-benzoyl group in the hydrazones can be replaced with an *N*-phenyl group; in this case the product, with otherwise the same substitution as in the product derived from the initial model substrate, was formed with 87% *ee* (Scheme 2a). This hydrazine product has no electron-withdrawing group on the nitrogen atom and slowly oxidizes in air, so it must be handled and stored under an inert atmosphere. The asymmetric hydrogenation of this type of hydrazone was not reported previously.

In one test case, the nickel catalyst loading was dropped to 0.5 mol%. Under these conditions, we obtained 1.19 g of the product with 96% *ee* (Scheme 2b).

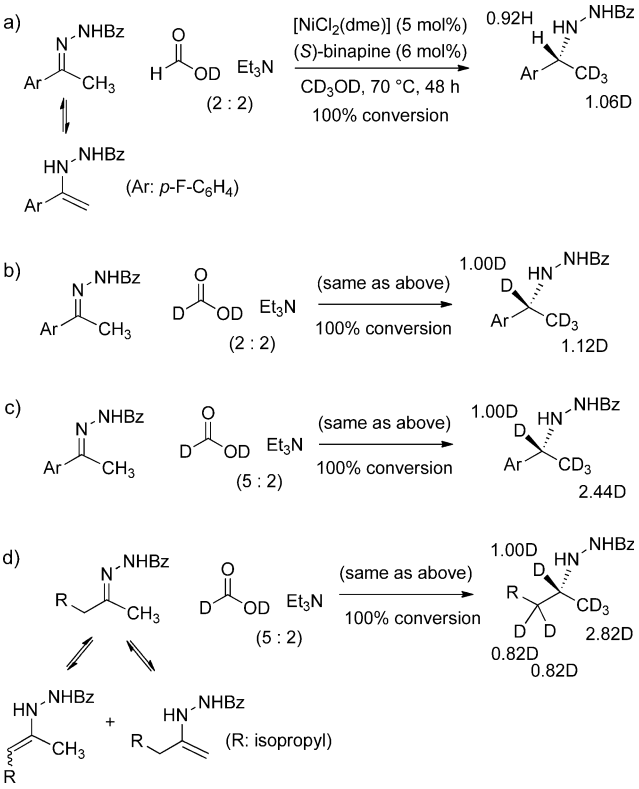
Differentiation of the *tert*-butyl and methyl groups in the hydrazone was successful with the binapine catalyst (Scheme 2c). However, the differentiation of *sec*-alkyl and methyl groups was challenging with binapine. When a josiphos ligand, CyPF-Cy (see Scheme 1), was used instead, good enantioselectivity was observed (Scheme 2d).

We also found that a related BPE catalyst enabled the hydrogenation of some benzosultams to give the desired products with more than 90% *ee* (Scheme 3).[32] Binapine afforded only moderate selectivity. Sodium naphthalide can cleave the C–S single bond in sulfonamides to give biarylmethylamines.[33] Under similar conditions to those in Scheme 3, the hydrogenation of the *N*-tosylketimine and the *N*-tosylhydrazone of acetophenone gave the desired products in only 30 and 40% *ee*.



Scheme 3. Transfer hydrogenation of benzosultams. The yields given are for the isolated product of a reaction carried out on a 0.2 or 0.5 mmol scale. (For the structure of the catalyst, see (*S*)-Ph-BPE in Scheme 1.)

To study the reaction mechanism, we conducted catalytic reactions with [D_1] and [D_2]formic acid (Scheme 4). Clearly, the formyl hydrogen atom of formic acid was donated as a hydride, presumably after decarboxylation at the nickel center. To our surprise, the methyl group of the hydrazine product was extensively deuterated; the extent of deuteration increased as the concentration of deuteron in the solution increased (Scheme 4c). When a dialkyl hydrazine was used, the product was extensively deuterated at both the α and the α′ positions (Scheme 4d). These observations can be best explained by prior equilibration of the imine and enamine tautomers of the hydrazone. An alternative pathway that involves direct hydride insertion into an enamine (an electron-rich olefin) is much less likely.



Scheme 4. Deuterium-labeling experiments.

We used the ONIOM-DFT method developed by Morokuma and co-workers[34] and focused on the hydride-insertion step between cationic [{(*S*)-binapine}(hydrido)nickel(II)]$^+$ and a bound *s-transoid* hydrazone (Figure 1). Several important conclusions were drawn: 1) The amide group of the hydrazone chelated readily to the nickel center. 2) Two diastereomeric transitional structures were 2.9 kcal mol^{-1} apart in energy, in agreement with the observed selectivity of 97% *ee* (*R*). The main pathway leading to the *R* isomer has an activation barrier of around 10 kcal mol^{-1} with the *s-transoid* conformer. 3) Paths of the less stable *s-cisoid*

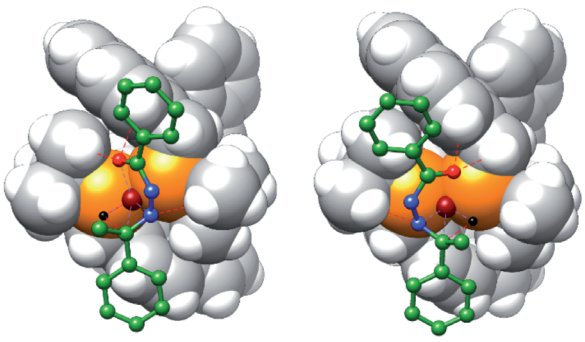


Figure 1. Transition structures TS-R (left) and TS-S (right) for hydride insertion by [{(*S*)-binapine}(H)Ni^{II}]$^+$ into a bound *s-transoid* hydrazone derived from acetophenone. (*S*)-Binapine is shown in space-filling mode and other TS atoms in ball-and-stick mode. The nickel atom is dark red, the hydride is black, and the oxygen, nitrogen, and carbon atoms of the hydrazone are red, blue, and green, respectively.

conformer were less favorable and had higher transition-state energies (2–3 kcal mol^{-1}) than those of the *s-transoid* conformer. 4) The path corresponding to the insertion of a neutral nickel(I) hydride was also examined, but the energy gap of the transition states was too small to account for the high enantioselectivity observed. 5) The facile decarboxylation of formate at a (binapine)nickel(II) center was found to produce carbon dioxide and a hydride ligand, so paths of direct formate addition are unlikely. 6) The phenyl ring of the benzamide fragment of hydrazone was not responsible for stereoinduction, as a high energy gap for insertion was also identified when this phenyl group was changed to a hydrogen atom.

The two transition-state structures reveal some interesting points: a) The bulky binapine ligand does not have a deep pocket or crevice. b) No severe contact between the hydrazone and the catalyst was seen, so a simple model based on steric repulsion seems unlikely. c) The Ni···O bond in TS-S is longer than in TS-R (2.7 versus 2.4 Å) owing to close contact with an aryl ring of binapine. d) Two *tert*-butyl groups of binapine slightly shielded the top-left and bottom-right quadrants. The shallow concave recess in TS-R accommodates better the *s-transoid* hydrazone than TS-S (shape complementarity). e) We observed a close CH···O contact between a *tert*-butyl group of binapine and the hydrazone in TS-R (2.4 Å) and a bond angle of about 160°. In TS-S, the CH···O interaction was highly bent and hence much weaker (2.6 Å and $<120°$).[35] Shape complementary and weak attractive interactions are the mainstay of enzymatic catalysis and drug–receptor binding, but they have rarely been seen in transition-metal catalysis.[36]

In conclusion, we have reported stereoselective nickel catalysts for the transfer hydrogenation of hydrazones and other ketimines. A family of strongly σ donating bisphosphines efficiently promoted the reductive process. In one test case, 200 turnovers were observed. Our DFT studies suggest that the nickel/binapine catalyst uses shape complementary and weak attractive interactions to effect asymmetric induction, instead of conventional steric repulsion.

Keywords: asymmetric catalysis · hydrazones · hydride insertion · nickel · transfer hydrogenation

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[37] CCDC 1047581 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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