Asymmetric Hydrogenation

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Nickel-Catalyzed Enantioselective Reductive Amination of Ketones with Both Arylamines and Benzhydrazide

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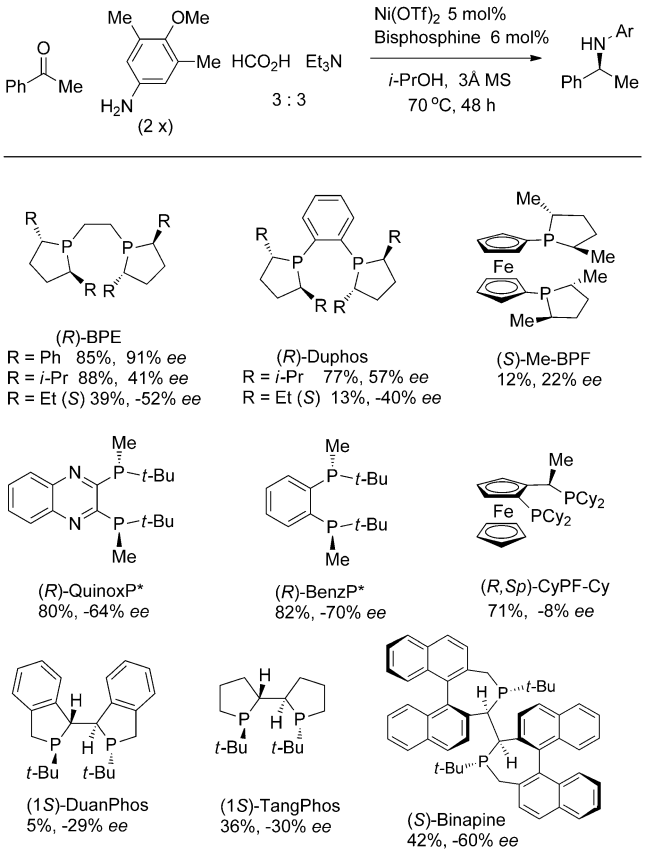
Abstract: *An asymmetric reductive amination of ketones using both arylamines and benzhydrazide in the presence of nickel catalysts was developed. A one-pot synthesis of tetrahydroquinoxalines was also developed starting directly from α-ketoaldehydes and 1,2-diaminobenzene. Formic acid was used as a safe and economic surrogate for high-pressure hydrogen gas. Strongly σ-donating bis(alkylphosphine)s are crucial ancillary ligands for both stereoselective hydride insertion and decarboxylation of the formate.*

Chiral alkylamines are present as structural motifs in many drugs and some agrochemicals. Classical resolution of racemic alkylamines[1] and transition-metal-catalyzed hydrogenation of ketimines and enamines[2] are two common methods used in the large-scale production of chiral amines. Hydrogenation catalysts based on expensive, highly toxic noble metals are often used, such as rhodium,[3] iridium,[4] ruthenium,[5] and recently palladium.[6] In active pharmaceutical ingredients, heavy-metal residues must be reduced to ppm levels, which incurs additional cost in waste treatment. In the past decade, chiral hydrogenation catalysts based on cheap and nontoxic iron with promising catalytic activity have emerged.[7]

Compared to the hydrogenation of ketimines and enamines, reductive amination directly uses ketones and bypasses the isolation and purification of ketimines, some of which are susceptible to hydrolysis.[8] However, most existing examples involve expensive noble-metal catalysts.[9] Moreover, arylamines have commonly been used owing to facile condensation to form ketimines or enamines. Recently, Beller et al. disclosed examples of reactions between aryl methyl ketones and aromatic amines under 50 bar of H_2 gas, using dual catalysis of an achiral iron catalyst (Knölker's complex) and a chiral phosphate counterion. The latter was the source of chirality during hydride transfer.[10] Reactions of aliphatic methyl ketones, however, only provided products in around 70% *ee*. In the past decade, chiral acids and hydrogen-bond donors have also been successfully used as organocatalysts in asymmetric reductive amination in the presence of organic hydrogen donors.[11]

Discrete nickel complexes of achiral phosphines and N-heterocyclic carbenes are known to show promising hydrogenation activity towards olefins[12] and imines.[13] The Hamada and Chirik groups have separately disclosed nickel catalysts with chiral bisphosphine ligands for the asymmetric hydrogenation of ketones[14] and α,β-unsaturated esters,[15] but high pressure (33–100 bar) H_2 gas was needed. Our group has also reported nickel-catalyzed transfer hydrogenation of enamides, conjugated olefins, and hydrazones,[16] using formic acid as a safe and cheap source of hydrogen.[17] In this work, we successfully applied nickel catalysis to reductive amination of ketones with both arylamines and benzhydrazide.

Initially, we attempted a model reaction between acetophenone and inexpensive 3,5-dimethyl-4-anisidine (Scheme 1). We observed facile reduction of the ketone by the nickel catalysts. To solve this problem, molecular sieves



Scheme 1. The effect of chiral bisphosphines in a model reductive amination of 3,5-dimethyl-4-anisidine and acetophenone (0.1 mmol scale).

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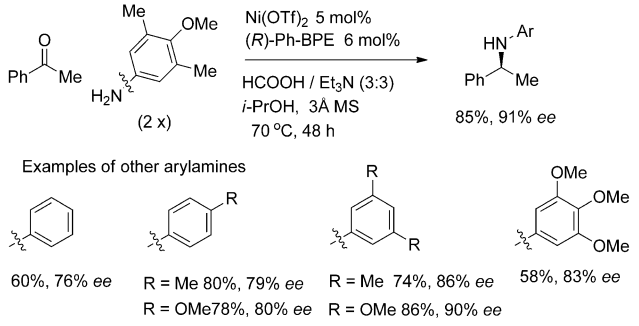
were add to promote prior formation of the ketimine. The use of alcohol solvents such as isopropanol and *n*-butanol was also critical to the formation of the amine product. Under the optimized conditions, the model reaction afforded the desired product in 85% yield and 91% *ee* in the presence of a nickel/Ph-BPE catalyst. Notably, when the model reaction was conducted in a one-pot manner, i.e., without pre-formation of the ketimine, the desired product was still obtained in 76% yield in the presence of molecular sieves (see the Supporting Information).

The ligand Ph-BPE was found to be the most stereoselective among the bisphosphines invented by Burk et al., while DuPhos and BPF were found to be less selective (Scheme 1).[18] QuinoxP* and BenzP*[3e,19] afforded good yields, but only moderate *ee* was obtained. We also tested several Josiphos ligands,[20] but they did not provide good *ee* values either. Other strongly donating bis(alkylphosphine)s developed by Zhang et al. were also tested, but they afforded unsatisfactory *ee* values. For example, a nickel catalyst with the ligand Binapine[21] resulted in only 60% *ee* in the model reaction, while DuanPhos and TangPhos led to low catalytic activity and less than 30% *ee*. Less-donating bis(arylphosphine)s such as BINAP, Segphos, and DIPAMP did not produce active catalysts at all.

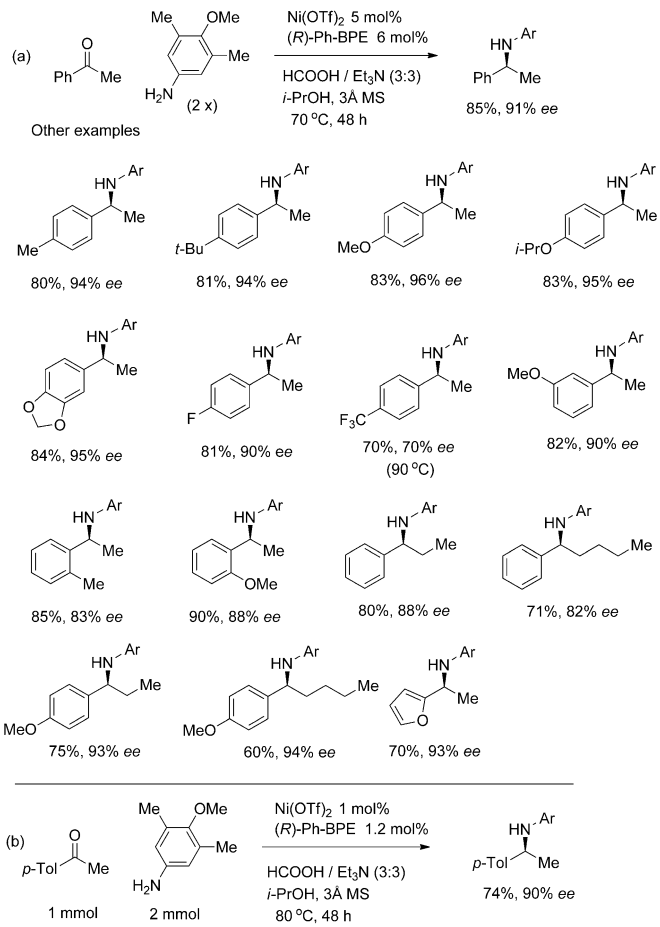
Regarding the choice of the amine component, parent aniline and *p*-anisidine gave products in 76 and 80% *ee* (Scheme 2). The *ee* value was improved to around 90% when



Scheme 2. Asymmetric reductive amination of acetophenone with several anilines (0.3 mmol scale).

bigger anilines such as 3,5-dimethoxyaniline and 3,5-dimethyl-4-anisidine were used. The anisidine fragment in the products can be easily removed by treatment with oxidants.[22] Notably, we found that *o*-tolylamine did not undergo the desired process.

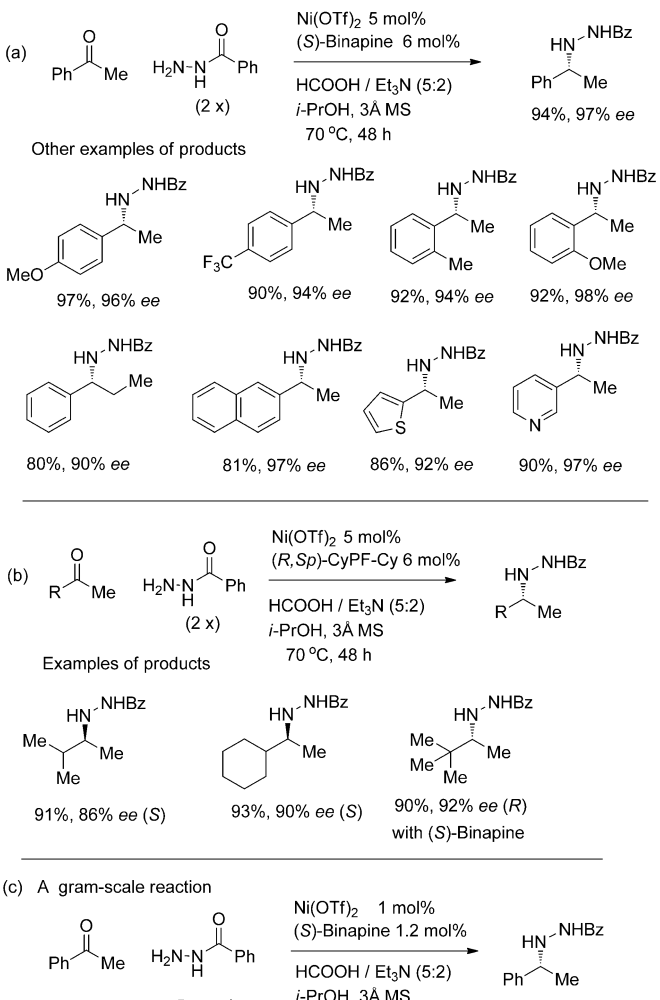
We next explored the scope with respect to the ketones under the optimal conditions (Scheme 3a). A series of aromatic ketones were readily aminated with good *ee* values. Both electron-donating and electron-withdrawing groups can be present on the aryl rings of the ketones. Furthermore, the catalytic process can be conducted with 1 mol% of the nickel catalyst (Scheme 3b). Unfortunately though, reactions of aliphatic methyl ketones gave very low selectivity (<20% *ee*) in combination with various arylamines.[23]



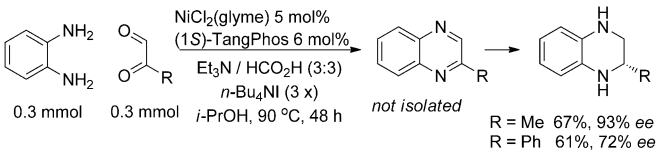
Scheme 3. Asymmetric reductive amination of aromatic ketones with 3,5-dimethylanisidine (0.3 mmol scale in most cases).

Next, we examined the reductive amination of ketones with benzhydrazide, a cheap amine source (Scheme 4a). To our satisfaction, a diverse set of aromatic ketones reacted efficiently to give *N*-benzoylhydrazine products with high *ee* values in the presence of a nickel/Binapine catalyst. All of the reactions were conducted under one-pot conditions with molecular sieves as a dehydrating agent. Thus, no prior formation of hydrazones was needed. For reactions of two aliphatic ketones, a Josiphos ligand, CyPF-Cy, afforded excellent stereoselectivity (Scheme 4b). In a test case, the nickel catalyst loading was reduced to 1 mol%, and the product was isolated in 95% yield and 97% *ee* on a 5 mmol scale (Scheme 4c). Further reducing the catalyst loading to 0.5 mol% resulted in 70% yield without any loss of *ee*. The resulting *N*-benzoylhydrazine products are crystalline and can be readily crystallized to boost optical purity. In addition, the N–N single bond in the products can be cleaved to release free alkylamines with SmI_2[4a] and Raney nickel.[24]

We also successfully performed double reductive amination to produce substituted tetrahydroquinoxalines directly (Scheme 5).[25] 1,2-Diaminobenzene and α-ketoaldehydes spontaneously condensed to form quinoxalines even without molecular sieves. The quinoxalines were hydrogenated by a nickel/TangPhos catalyst to give products in moderate to



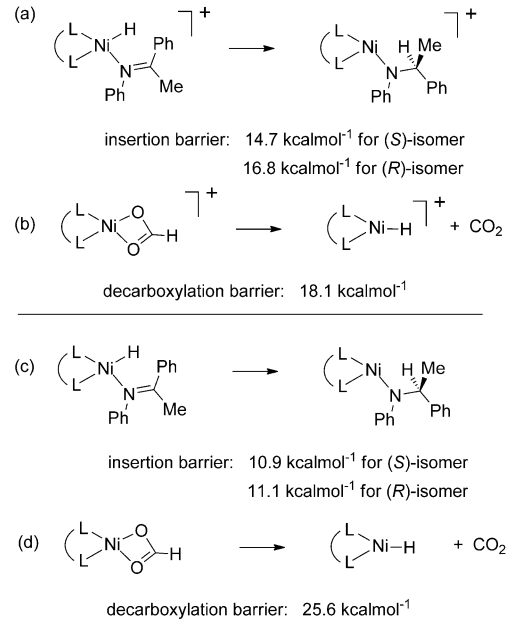
Scheme 4. Asymmetric reductive amination of ketones with benzhydrazide (0.3 mmol scale in most cases).



Scheme 5. Asymmetric reductive amination of 1,2-diaminobenzene with α-ketoaldehydes (0.3 mmol scale).

good *ee* values depending on the C2 substituents.[26] *n*-Bu_4NI was added to improve the *ee* and to minimize N-formylation of the products, a side reaction. The hydrogenation occurred on the less substituted C=N bond first.

We used the ONIOM(QM:QM′) method developed by Morokuma et al.[27] to simulate hydride insertion of a cationic complex of [(*R*)-Ph-BPE)](hydrido)nickel(II) into a bound *N*-phenylketimine derived from acetophenone (Scheme 6a). The insertion step sets the configuration of the new stereocenters. We determined two diastereomeric transition-state structures, and their energies were 2.1 kcal mol^{-1} apart, which



Scheme 6. Calculations on both steps of hydride insertion and decarboxylation in nickel catalysis where L–L is (*R*)-Ph-BPE.

is consistent with the observed 76% *ee* (*S*) as indicated in Scheme 2. The pathway leading to the major (*S*) isomer had an energy barrier of 14.7 kcal mol^{-1}. We also simulated the decarboxylation of a cationic (formyl)nickel(II) complex to form the hydride species and its energy barrier was 18.1 kcal mol^{-1} (Scheme 6b). In comparison, in possible pathways of neutral (hydrido)nickel(I) complexes, the energy gap between the two insertion transition states was too small to account for the observed *ee* value (Scheme 6c). Furthermore, decarboxylation of neutral (formyl)nickel(I) entailed an exceedingly high energy barrier of 25.6 kcal mol^{-1} (Scheme 6d), which convinced us to discount the nickel(I) pathways.

Close examination of two insertion transition states of cationic (hydrido)nickel(II) complexes revealed interesting insight into the origin of stereoselectivty (Figure 1). In the transition states (TSs), two phenyl rings of the chiral phospholanes point to the front and constitute a very restricted chiral pocket around the nickel center. In TS-*S*, which leads to the major enantiomer (Figure 1a), the *E*-ketimine fits comfortably into the pocket. In TS-*R*, which leads to the minor enantiomer (Figure 1b), to our surprise, no close contact was identified between the catalyst and the ketimine. Instead, we found that the N-phenyl ring of ketimine was forced out of coplanarity with the C=N bond of the imine, so as to avoid steric repulsion with the catalyst in the bottom-left space. This clearly contributes to destabilization of the transition state TS-*R* on a minor pathway. As shown in Scheme 2, larger N-aryl rings in anilines such as 3,5-dimethylanisyl improve the stereoselectivity in the model reaction. This can be explained by destabilization of the unfavorable transition state TS-*R* due to steric effects. In comparison, in our previous report on nickel/Binapine-catalyzed hydrogenation of hydrazones, the hydrazones

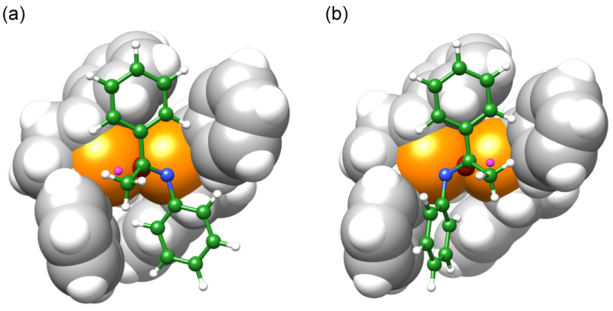


Figure 1. Transition-state structures TS-*S* (a) and TS-*R* (b) for hydride insertion of cationic [(*R*)-Ph-BPE](hydrido)nickel(II) into a π-bound *N*-phenylketimine to give the major (*S*) and minor (*R*) isomers, respectively (see Scheme 6a). The ligand Ph-BPE is shown in space-filling mode while other molecules are shown as ball-and-stick models. Nickel is shown in dark red, hydride in pink, phosphorus in orange, nitrogen in blue, and carbon atoms of the ketimine in green.

chelated cationic hydridonickel centers to form 5-coordinated species, and stereoselective hydride insertion was facilitated by a weakly attractive CH···O interaction instead.[16c]

In conclusion, we have developed an asymmetric reductive amination of ketones using both arylamines and benzhydrazide in the presence of nickel catalysts. A one-pot synthesis of tetrahydroquinoxalines was also developed starting directly from α-ketoaldehydes and 1,2-diaminobenzene. Formic acid was used as a safe and economic surrogate for high-pressure hydrogen gas. Strongly σ-donating bis(alkylphosphine)s were crucial ancillary ligands for both stereoselective hydride insertion and decarboxylation of the formate.

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Keywords: chiral alkylamines · nickel · reductive amination · synthetic methods · transfer hydrogenation

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Communications

Asymmetric Hydrogenation

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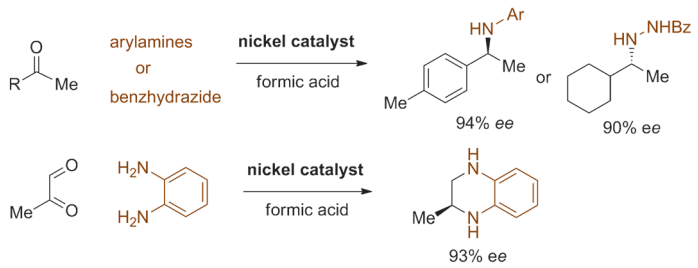
Nickel-Catalyzed Enantioselective Reductive Amination of Ketones with Both Arylamines and Benzhydrazide



Reducing costs: Reductive amination of ketones with both arylamines and benzhydrazide was realized in the presence of catalysts based on nickel rather than expensive noble metals. Formic acid was used as a safe and cheap surrogate for high-pressure hydrogen gas.