Asymmetric Hydrogenation

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Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Olefins for the Synthesis of α- and β-Amino Acids**

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Abstract: *The field of asymmetric (transfer) hydrogenation of prochiral olefins has been dominated by noble metal catalysts based on rhodium, ruthenium, and iridium. Herein we report that a simple nickel catalyst is highly active in the transfer hydrogenation using formic acid. Chiral α- and β-amino acid derivatives were obtained in good to excellent enantioselectivity. The key toward success was the use of the strongly donating and sterically demanding bisphosphine Binapine.*

Asymmetric olefin hydrogenation is commonly practiced in industry for the large-scale synthesis of pharmaceutically active ingredients.[1] Often rhodium-, ruthenium-, and iridium-based catalysts are used. Excellent stereoselectivity can be achieved by a judicious choice of suitable phosphorus ligands and the catalyst loading can be lowered for an economic application at large scale.[2] However, these heavy metal catalysts are expensive, toxic, and damaging to the environment. Furthermore, their reserves in earth's crust are depleting. Recently, there is renewed interest in developing cheap, abundant first-row metal catalysts for the asymmetric hydrogenation of prochiral olefins. For example, Chirik et al. reported a cobalt-catalyzed asymmetric hydrogenation of substituted styrenes and dehydroaminoesters with good enantioselectivity (Figure 1).[3] Unfortunately, in the first example, an air-sensitive cobalt complex of a bisiminopyridine must be used and in both cases the scope of olefins was quite limited.

Herein, we disclose a simple nickel/Binapine catalyst for asymmetric transfer hydrogenation reactions leading to α- and β-amino acids. Formic acid is used as the hydrogen equivalent.[4] Thus, safety hazard associated with the storage and handling of high-pressure hydrogen gas is avoided. In addition, nickel is 100- to 1000-fold cheaper than ruthenium, rhodium, and iridium, when the price of their chloride salts is compared.[5]

Heterogeneous nickel catalysts modified by tartaric acid have been reported to afford more than 90% *ee* in the directed hydrogenation of selected ketones such as β-ketoesters.[6] Recently, Hamada et al. described a nickel-catalyzed asymmetric hydrogenation of α-amino-β-ketoesters using 10 atm of H_2 and obtained around 90% *ee* under conditions of dynamic kinetic resolution.[7] At present, a highly asymmetric (transfer) hydrogenation of prochiral olefins using nickel catalysts has not been realized.[8]

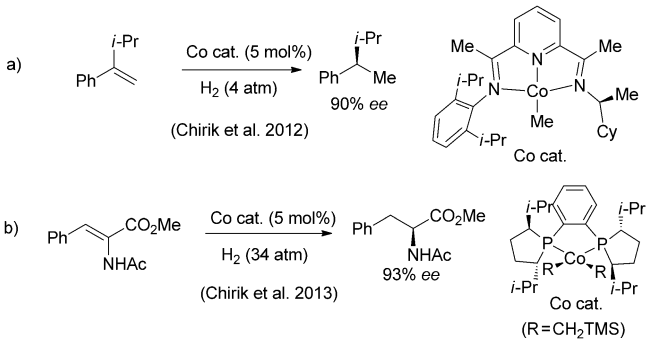

Figure 1. Cobalt-catalyzed asymmetric hydrogenation of olefins by Chirik et al.

β-Amino acids are important building blocks for the synthesis of pharmaceuticals, e.g., β-lactam antibiotics. They are also monomers of peptidomimetics that are resistant to enzymatic degradation.[9] β-Amino acid derivatives have been synthesized by Rh- or Ru-catalyzed asymmetric hydrogenation of β-acetamido- and β-amidoacrylates.[10] The metal-catalyzed asymmetric transfer hydrogenation using formic acid or isopropanol to prepare amino acid derivatives was rarely studied and afforded poor stereoselectivity.[11] In our model hydrogenation reaction of α,β-dehydro-β-acetaminobutyrate (Figure 2), we found that nickel catalysts ligated by highly electron-rich and sterically demanding bisphosphines were catalytically active. In particular, (*S*)-Binapine afforded good conversion and 96% *ee*. (*S*)-Binapine was prepared through the copper-mediated homocoupling of 1,1′-binaphthophosphepine sulfide by Xumu Zhang et al.[12] Two related bisphosphines TangPhos and DuanPhos were less selective (35% *ee* and 71% *ee*). Mark Burk's ligands including Ph-BPE, Me-DuPhos, and Me-DPF were also catalytic active, but the selectivity was not good.[13] Imamoto's *P*-chiral bisphosphine QuinoxP* afforded 72% *ee*.[14] One of the Josiphos ligands was catalytically active but the selectivity was only moderate.[15] Other less donating phosphine ligands, such as BINAP, Segphos, DIPAMP, and PHOX, were completely inactive. Many other metal salts of iron, cobalt, and copper were tested together with Binapine, but they were inactive in the model reaction (see the Supporting Information).

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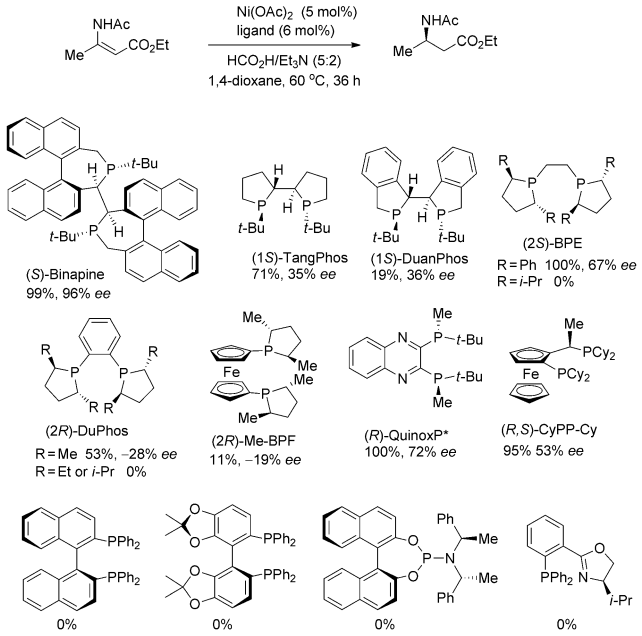
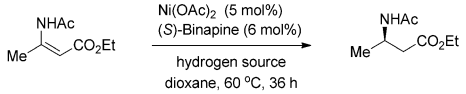


Figure 2. The performance of chiral phosphines in a model reaction of dehydro-β-acetamidobutyrate.

Table 1: The effect of the hydrogen source.



Entry	Hydrogen source	Conv. [%]	Yield [%]	*ee* [%]
1	HCO_2H:Et_3N 2:2	57	57	83
2	2:5	55	55	79
3	3:2	78	78	90
4	5:2	99	99	96
5	$NaCO_2H$ or NH_4CO_2H	0	0	–

A 5:2 molar mixture of HCO_2H and Et_3N was optimal for both catalytic activity and enantioselectivity in the model reaction (entry 4, Table 1). For example, when the stoichiometry was changed to 2:2, the reaction afforded only 57% yield and 83% *ee* (entry 1). No hydrogenation was observed at a hydrogen pressure of 10 bar and a temperature of 80°C.

In many solvents including THF, dioxane, toluene, MeOH, EtOH, *i*-PrOH, EtOAc, DMF, and dichloroethane, the reaction proceeded smoothly and provided similar results. For example, the model reaction was slightly faster in *i*-PrOH than in dioxane, albeit with a slight drop of *ee* (93% *ee*).

The scope of olefins that can be hydrogenated by the Ni/Binapine catalyst was broad (Figure 3). Various aryl and alkyl groups can be present at the β position. Olefins with both electron-rich and electron-poor aryl groups provided the corresponding products in very high *ee*. Importantly, some heteroaryl rings were also tolerated. Both amides and imides seemed to function as directing groups and induced excellent *ee*. In one example with a β-anilino group, only 30% *ee* and low yield (10%) was obtained due to the in situ hydrolysis of

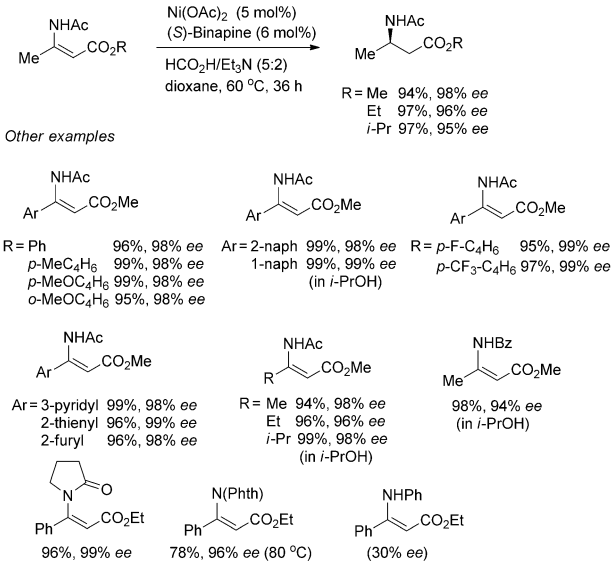


Figure 3. Asymmetric transfer hydrogenation for the synthesis of β-acylamidoesters.

the enamine group. The (*E*)-isomer of the model olefin was also efficiently hydrogenated, but only 44% *ee* was observed at 60°C. This is probably caused by two competing insertion modes for hydride insertion on the nickel center.

The Ni/Binapine catalyst can also be successfully applied to the synthesis of α-acetamidoesters in more than 80% *ee* (Figure 4). We found that an equimolar mixture of formic acid

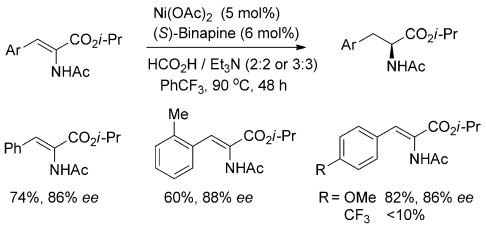


Figure 4. Asymmetric transfer hydrogenation for the synthesis of α-acetamidoesters.

and Et_3N was important to ensure good *ee*. In 1,4-dioxane, only low conversion was obtained. Changing the solvent to $PhCF_3$ or toluene improved the conversions. Surprisingly, a substrate bearing an electron-deficient aryl group did not react.

To probe the reaction mechanism of the transfer hydrogenation of β-acetamidoacrylates, we conducted deuterium-labeling experiments using [D_1] and [D_2]formic acid. When [D_1]formic acid was used, no deuteron was added at the β position (Figure 5a). Interestingly, the deuteron was incorporated at both α positions with a 3:1 *anti*/*syn* preference.[16] When [D_2]formic acid was used, deuterium was added to both α positions and to the β position (Figure 5b). This result suggests that a decarboxylation of the formate produces a nickel hydride, which then adds to the β position to form a nickel enolate species. Protonation of the nickel enolate is in

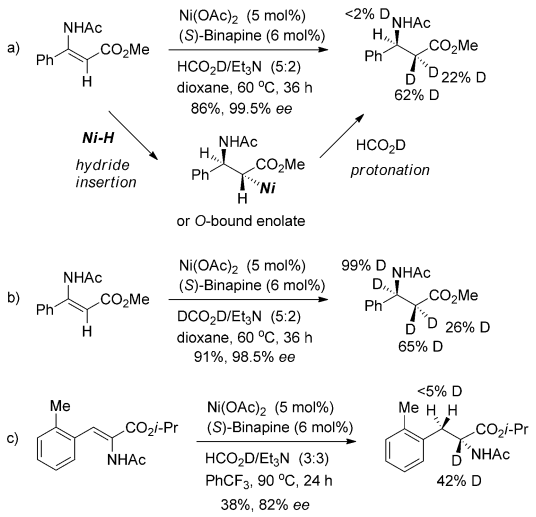


Figure 5. Deuterium-labeling experiments of the transfer hydrogenation.

this case not *syn*-selective. Thus, no concerted C–H reductive elimination took place on the nickel center. The nickel catalysis is mechanistically distinct from the rhodium dihydride[17] and ruthenium monohydride pathways,[18] both of which led to a *syn*-insertion of dihydrogen. The incorporation of deuterium at the α position is less than 100%, which is probably caused by a trace amount of water. No further H/D exchange was observed after the product was formed.

Similarly, when [D_1]formic acid was used in the hydrogenation of an α-acetamidoacrylate and the reaction was stopped after 24 h at 90 °C after a partial conversion, the deuteron was found almost exclusively at both α positions (Figure 5c). Thus, the nickel hydride, which was derived from formyl hydrogen, added selectively to the β position of the α-acetamidoacrylate. An equimolar mixture of formic acid and Et_3N formed in situ a bulky triethylammonium cation, which was responsible for the stereoselective protonation of the nickel enolate in this case.

In summary, we have developed a Ni-catalyzed asymmetric transfer hydrogenation to access both β- and α-amino acids in good to excellent *ee*. A strongly σ-donating and sterically demanding bisphosphine, Binapine, was necessary to form a highly active and stereoselective catalyst. Deuterium labeling experiments suggest that the transfer hydrogenation proceeds through an asymmetric hydride insertion followed by a protonation of the nickel enolate species.

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