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Asymmetric Umpolung Hydrogenation and Deuteration of Alkenes Catalyzed by Nickel

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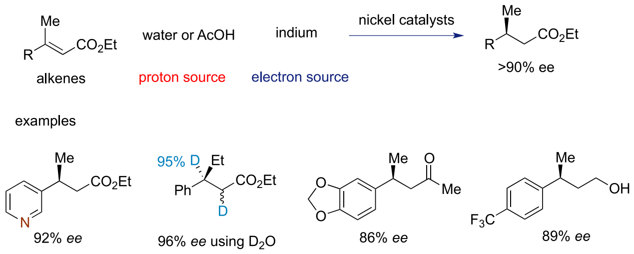
ABSTRACT: Nickel-catalyzed asymmetric hydrogenation of several types of alkenes proceeds in high enantioselectivity, using acetic acid or water as the hydrogen source and indium powder as electron donor. The scope of alkenes herein include α,β-unsaturated esters, nitriles, and ketones as well as allylic alcohols. Asymmetric deuteration of α,β-unsaturated esters is also achieved with deuterated water, the cheapest deuterium source.



Asymmetric hydrogenation uses transition-metal catalysts to add hydrogen gas to unsaturated bonds (Figure 1a). It has become one of the leading technologies for the production of chiral drugs on large scales.[1] Traditionally, noble metal catalysts based on Rh, Ir, and Ru are dominant working horses for these processes with H_2 pressure ranging from 1 to 100 bar. High-pressure hydrogen gas and pressurized hydrogen liquid are severe safety hazards during transport, storage, and use. Alternatively, formic acid and alcohols have been successfully developed as safe, easy-to-handle hydrogen sources in asymmetric transfer hydrogenation catalyzed transition metals (Figure 1b).[2] In recent years, Hantzsch esters and other organic hydride donors are also employed in asymmetric organocatalytic reduction.[3] Moreover, hydroboration and hydrosilylation are often regarded as equivalent of the hydrogenation reaction of double bonds, after hydrolytic release of products (Figure 1c).[4]

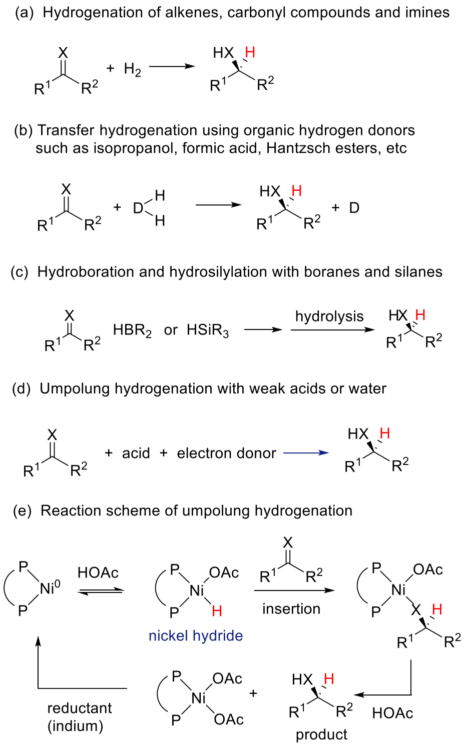


Figure 1. Different types of hydrogenation and reaction design of umpolung hydrogenation

Recently, water in combination with diboron[5] or disilane[6] reagents was used in Pd- and Ru-catalyzed hydrogenation of alkenes, alkynes, imines, and heteroarenes, as a safe and easy-to-handle alternative to hydrogen gas. In 2010, Zhou et al. reported the first example of iridium-catalyzed asymmetric hydrogenation of heteroaromatic compounds, using a combination of water and disilane.[7] In 2019, Fan et al. also disclosed Pd-catalyzed enantioselective hydrogenative ring opening of hetereobicyclic alkenes, by employing water and zinc powder.[8] Lately, water and diboron reagents were also successfully employed in Pd-catalyzed asymmetric reductive Heck cyclization.[9]

Herein, we describe the first example of asymmetric hydrogenation of several types of alkenes, using a combination of water or weak acids as hydrogen source and indium powder as ultimate electron donor (Figure 1d).[10] Thus, no high pressure hydrogen gas is needed, which is a safety hazard

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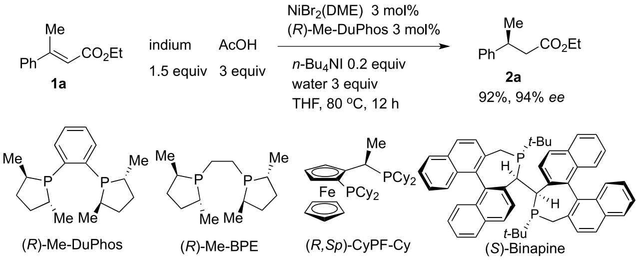
during transport, storage, and use. We employed homogeneous nickel catalysts ligated by strongly donating diphosphines for their proven catalytic activity in hydrogenation under high pressure of H_2[11] and transfer hydrogenation using formic acid.[12] Nickel is also abundantly present in Earth's crust, in contrast to the scarcity of rare noble metals that are often used in asymmetric hydrogenation, such as Rh, Ir, and Ru.

Moreover, in our previous studies of nickel-catalyzed transfer hydrogenation using formic acid, several pieces of evidence suggested reversible deprotonation of a cationic nickel(II) hydride species by a weak base, such as formate ion, to produce a nickel(0) complex in the catalytic mixture.[12] Combining with the information, we designed asymmetric umpolung hydrogenation using water or weak acids as hydrogen source (Figure 1e). A nickel(0) complex of a chiral bisphosphine is reversibly protonated by a weak Brønsted acid, e.g., acetic acid, to form a nickel hydride species[13] which was known to insert into polar alkenes and ketimines. After hydrolytic release of the product, the nickel(II) catalyst is reduced back to nickel(0) by a terminal electron donor, e.g., indium powder. The challenge is that the weak acid in the reaction must be compatible with indium powder, and at the same time, it should be acidic enough to effect reversible protonation of the nickel(0) complex to access the key nickel hydride species for catalytic insertion.

Initially, we used (*E*)-ethyl 3-methylcinnamate as a model alkene to identify suitable nickel catalysts and reaction conditions (Table 1). After many trials, we successfully established an optimized condition consisting of an in situ formed nickel catalyst of Me-DuPhos, 3 equiv of glacious acetic acid, 3 equiv of water, indium powder, and a catalytic amount of $n\text{-Bu}_4\text{NI}$ in THF. The conversion was >90% after 12 h at 80 °C. $n\text{-Bu}_4\text{NI}$ was critical to the good conversion, without which only 29% yield was obtained (entry 2). The iodide anion helped to form a trimeric cationic complex $\{[(\text{DuPhos})\text{Ni}(\text{OAc})]_3\text{I}\}^{2+}$ as the resting state of the catalyst, as judged by ^{31}P NMR spectroscopy.[11b] Combinations with other metal powder or other weak acids were evaluated. For example, manganese and zinc led to the product in lower yields but in similar ee values; when magnesium powder was used, the ee was significantly different (entries 3−5). There may be a noncatalytic background reduction caused by Mg powder. Weak Brønsted acids such as acetic acid and pivalic acid worked well in this reaction (entries 1 and 6), but strong *p*-tosylic acid reacted directly with indium powder to generate hydrogen gas, which short-circuited the productive pathway (entry 7). We found that acetic acid in THF cannot be replaced by water alone (entry 8). In a control experiment, we found no hydrogenation occurred even when 100 psi of hydrogen gas was applied, ruling out the involvement of hydrogen gas in this reaction. Furthermore, a catalytic amount of acetic acid (0.2 equiv) in water also worked well. The acid, also serving to activate indium powder, was necessary for the hydrogenation (entry 9). With regard to the choice of chiral phosphines, Me-Duphos proved optimal which afforded 94% ee.[12b,14] In THF, a small amount of water was needed. For example, full conversion was detected in the presence of 3 equiv of water (entry 1), whereas only 34% conversion and 13% yield of **2a**were seen in the absence of added water. Other chelating alkylphosphines were either less stereoselective (entry 10) or did not form active nickel catalysts (entries 11−13). The loading of the nickel catalyst can be decreased to 1 mol % in ethanol to give **2a** in 86% yield and 92% ee (see the Supporting Information).

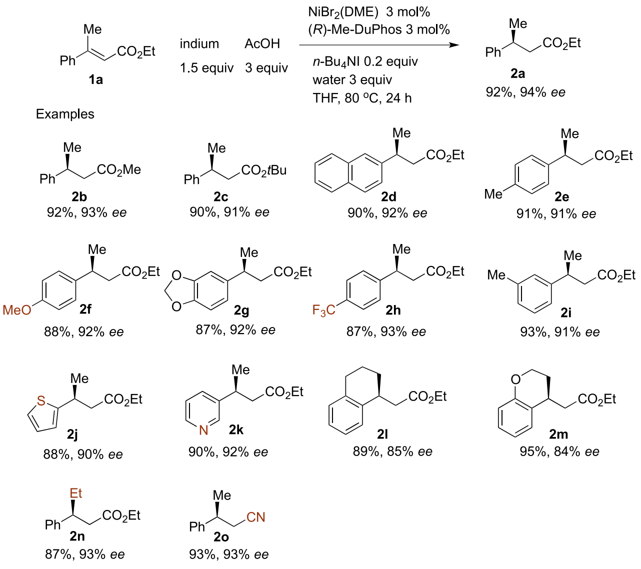
Table 1. Optimizations of Reaction Conditions



entry	change of conditions	yield (%)	ee (%)
1	none	92	94
2	no *n*-Bu$_4$NI	29	93
3	Mg instead of In	39	60
4	Mn instead of In	39	89
5	Zn instead of In	10	88
6	PivOH instead of AcOH	77	92
7	*p*-TsOH (3 equiv) instead of AcOH	<5	-
8	water (3 equiv); no AcOH	<5	-
9	AcOH (0.2 equiv) in water	98	92
10	(*R*)-Me-BPE as ligand	72	86
11	(*R*)-Et-DuPhos as ligand	0	-
12	(*R*,*Sp*)-CyPF-Cy as ligand	0	-
13	(*S*)-binapine as ligand	0	-

With the nickel catalyst of Me-DuPhos in hand, we examined the scope of *α*,*β*-unsaturated esters (Scheme 1). Various (*E*)-3-methylcinnamates carrying 3-aryl groups with different electronic properties were hydrogenated in high conversion and >90% ee in most cases. In comparison, (*Z*)-isomers of **3** led to much lower ee values. Moreover, heterocycles such as thiophene and pyridine were well tolerated at *β* positions of the acrylates (**2j** and **2k**). Additionally, two exocyclic alkenes reacted smoothly (**2l** and **2m**). Notably, a *β*,*β*-disubstituted acrylonitrile also provided the corresponding product in good yield and excellent ee value

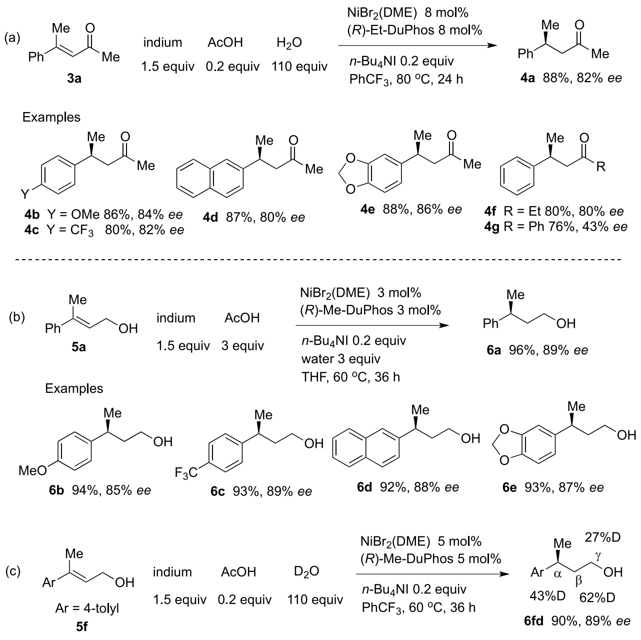
Scheme 1. Asymmetric Hydrogenation of *α*,*β*-Unsaturated Esters and Nitriles



(**2o**). We noticed that the reaction was sensitive to steric effects; for example, cinnamates having isopropyl or *t*-butyl groups at the β position had much slower conversions. Nitroarenes cannot survive the reductive conditions.

The umpolung hydrogenation also gave satisfactory results with two other types of alkenes, which did not give good results under nickel-catalyzed transfer hydrogenation using formic acid.[11] For example, conjugated enones resulted in competition of carbonyl reduction[15] and conjugate reduction in the latter conditions. In comparison, under umpolung hydrogenation using a nickel/Me-Duphos catalyst and 3 equiv of acetic acid in THF (see Scheme 1), enone **3a** led to selective conjugate hydrogenation surprisingly, albeit with slow conversion and moderate 70% ee. Changing the procedure using 0.2 equiv of acetic acid and 110 equiv of water in $PhCF_3$ accelerated the conversion, while the use of a nickel catalyst of Et-DuPhos increased the ee to 82% (Scheme 2b). *n*-Bu_4NI was crucial, without which the conversion was much lower. The optimized condition was then applied to other enones to give products **4** in >80% ee.

Scheme 2. Asymmetric Hydrogenation of *α,β*-Unsaturated Ketones and Allylic Alcohols

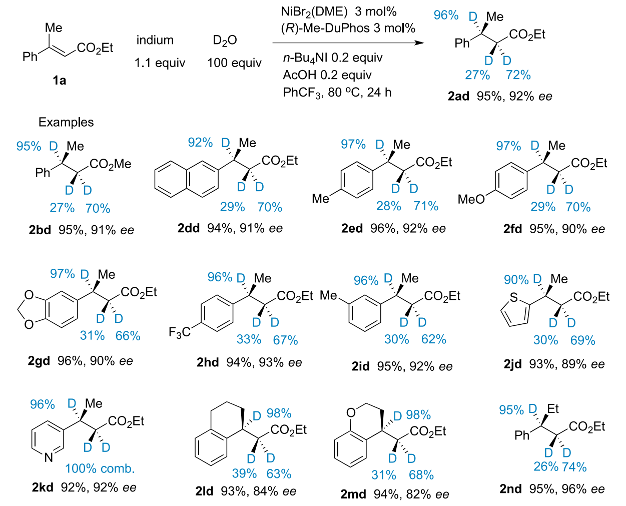


Furthermore, 3,3-disubstituted allylic alcohols **5**, which was unreactive under nickel-catalyzed transfer hydrogenation using formic acid, were suitable substrates under conditions of umpolung hydrogenation to products **6** in >85% ee (Scheme 2b). Notably, electronically unactivated styrenes did not react at all. When deuteration of allylic alcohol **5f** was attempted in 110 equiv of D_2O, α, β, and γ positions of product **5fd** were 43%, 62%, and 27% deuterated, respectively (Scheme 2c). This suggests that part of the product was derived from dehydrogenation of the carbinol group of **5f**, nickel hydride insertion of the resulting enal, and final nickel deuteride deuteration of the aldehyde. A small amount of the enal was indeed detected in the reaction mixture.

Deuterated compounds are often used to determine metabolic fates of drugs during drug discovery and development. Deuteration is also an indispensable tool for mechanistic investigation of catalytic and enzymatic reactions. Furthermore, deuteration of medicines at metabolizable positions can slow down oxidative degradation of drugs by P450 enzymes and thus elongate their half-lives in body, with minimal effects on binding affinity and toxicity. As a result, deuterated drugs may allow a lower dosage to be used with reduced toxicity of drugs.[16] Deuterated water is the cheapest deuterium source.

We have successfully developed a procedure for asymmetric deuteration of α,β-unsaturated esters (Scheme 1),[17] by using D_2O and a catalytic amount of HOAc in $PhCF_3$. To our gratification, product **2ad** was produced in 92% ee with 96% deuterium content at the β position. The ratio of deuteriation at two α positions was around 3:1, reflecting the facial selectivity of protonation of the putative O-bound nickel enolates after insertion. Notably, elongating the reaction time did not change the deuterium content at α positions, indicating that no further H/D exchange occurred between the product and D_2O in the reaction mixture. The deuteration procedure was applied to the other unsaturated esters with an excellent level of deuterium incorporation (Scheme 3). Close-to-unity deuterium content was detected in both β and α positions.

Scheme 3. Asymmetric Deuteration of *α,β*-Unsaturated Esters with D_2O



In summary, we reported nickel-catalyzed asymmetric umpolung hydrogenation of several types of alkenes, including α,β-unsaturated esters, nitriles, and ketones as well as allylic alcohols. Weak Brønsted acids such as acetic acid and water were successfully used as a hydrogen source, while indium powder was employed as the terminal electron source. Asymmetric deuteration of β,β-disubstituted acrylates using the cheapest deuterium source, deuterated water, was also achieved.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00112.

Additional experimental details (PDF)

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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