Organic LETTERS

Letter

pubs.acs.org/OrgLett

N,N-Dimethylformamide as Hydride Source in Nickel-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Esters

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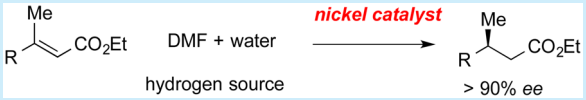
Supporting Information

ABSTRACT: Asymmetric transfer hydrogenation of α,β-unsaturated esters is realized by using a nickel/bisphosphine catalyst and *N,N*-dimethylformamide (DMF) as the hydride source.



Asymmetric hydrogenation is an industrially important process in the production of chiral drugs, fragrance, and agrochemicals.[1] Today, enantioselective hydrogenation of prochiral olefins mostly relies on metal catalysts of heavy noble metals including Rh,[2] Ru,[3] Ir,[4] and lately Pd.[5] The expensive heavy metals not only incur high costs in the production process but also require recovery and recycling of the toxic metals for environmental reasons. In addition, these noble metals are produced in small amounts each year and are facing quickly depleting reserves. For example, only 3 tons of iridium is produced a year worldwide, of which only 10% is committed to chemical catalysis.

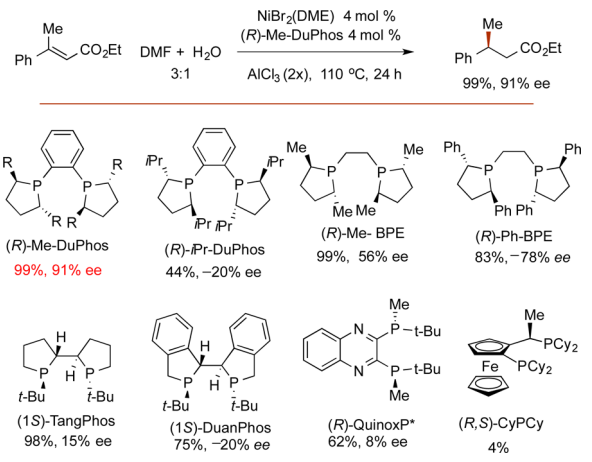
In comparison, first-row metal catalysts of abundant metals such as copper, nickel, and iron have gained renewed interest in recent years. They are being produced in millions of tons every year, and they are thousands-fold cheaper than noble metals. Moreover, noble metals have much higher carbon footprints than Earth-abundant metals due to complex extraction and purification processes; for example, nickel and palladium have carbon footprints of 7 and 6649 CO_2 equiv, respectively. Notably, oral exposure limits of metal residues in active pharmaceutical ingredients are not very different, for example, 25 ppm for nickel and 10 ppm for palladium, respectively.[6]

In the past decade, Beller, Morris, and others reported iron catalysts for asymmetric hydrogenation of ketones and ketimines,[7] but so far only asymmetric hydrogenation of prochiral olefins has been reported.[8] Recently, the Chirik group disclosed cobalt−bisphosphine catalysts for asymmetric hydrogenation of aryl olefins and enamides.[9] Recently, the same group also reported a nickel/DuPhos catalyst for hydrogenation of α,β-unsaturated esters in good ee, but 33 bar of hydrogen gas was needed.[10] Our group recently reported nickel/bisphosphine catalysts for asymmetric transfer hydrogenation of activated olefins, ketimines, and hydrazones.[11] We used easy-to-handle formic acid as a safe and cheap hydrogen source.[12]

Herein, we disclose our new finding that *N,N*-dimethylformamide (DMF) served as an alternative hydrogen source in asymmetric hydrogenation of α,β-unsaturated esters. DMF is a common solvent[13] and was used in reductive synthesis of nanoparticles of silver, gold, and platinum.[14]

We discovered that a nickel catalyst supported by Me-DuPhos, a chiral bisphopshine originally invented by Burk,[15] afforded good stereoinduction in a model reaction (Scheme 1).

Scheme 1. Performance of Chiral Bisphosphines in a Model Reaction of (*E*)-α,β-Methylcinnamate (Calibrated GCYields)



The performance of other chiral bisphosphines was rather unsatisfactory. For example, two related ligands, Me-BPE and Ph-BPE, gave only 56% ee and 78% ee, respectively. Additionally, *P*-chiral bisphosphines including TangPhos, DuanPhos, and QuinoxP* provided less than 20% ee.[16] Other less donating bis(arylphosphine)s such as BINAP, chirophos, and segphos were completely inactive in the test case.

We found that a 3:1 mixture of DMF and water was sufficient to work as the hydrogen source in the model reaction (Table 1). If dry DMF was used, no conversion was seen (entry 1). Additionally, when we changed the major solvent of DMF to DMA, DMSO, dioxane, or alcohols, no reaction was detected by GC, either (entries 2−4). We also changed the $AlCl_3$

Received: September 5, 2016

DOI: 10.1021/acs.orglett.6b02662
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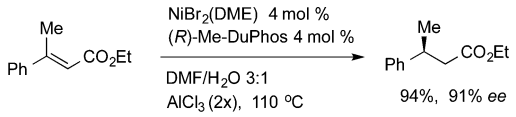
Table 1. Effect of Solvents and Additives in a Model Hydrogenation of Ethyl (*E*)-α,β-Methylcinnamate (Calibrated GC Yields)



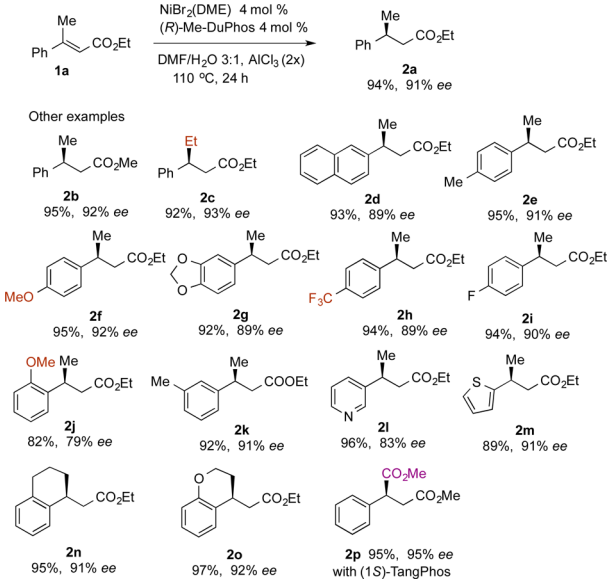
standard conditions

entry	changes in standard conditions	conv (%)	yield (%)	ee (%)
1	DMF as solvent	0	0	
2	3:1 DMA/H_2O	0	0	
3	3:1 DMSO/H_2O	0	0	
4	3:1dioxane/H_2O	0	0	
5	$BF_3{\cdot}OEt_2$	70	66	27
6	$InCl_3$ (2×)	100	98	81
7	$ZnCl_2$ (2×)	93	90	81
8	$Zn(OTf)_2$ (2×)	41	39	81
9	*p*-tolSO_3H (0.2×)	97	94	78
10	CF_3SO_3H (0.2×)	67	63	81
11	HCl (2×)	51	50	89

additive to other Lewis acids and Brønsted acids, but only inferior results were obtained. Notably, in the presence of $InCl_3$ and $ZnCl_2$, the model reactions still proceeded in good yields, but the ee values were only around 80% (entries 6 and 7). When HCl was used as the additive, only half conversion was detected under the same conditions, although the ee was almost as good as the optimized conditions (entry 11).

With the optimized conditions in hand, we explored the scope of olefins. α,β-Unsaturated esters having the aryl rings *trans* to the ester groups reacted well and gave high ee values (Scheme 2). Both electron-rich and -poor substituents were tolerated on the aryl rings. The *o*-methoxy group (**2j**) can be present on the aryl rings, while pyridyl and thienyl rings (**2l** and **2m**) were tolerated, too. Additionally, two cyclic olefins were also successfully hydrogenated with good ee values (**2n** and **2o**). Replacement of the β-aryl rings with alkyl groups such as benzyl and cyclohexyl led to moderate stereoselectivity,

Scheme 2. Examples of Transfer Hydrogenation (Isolated Yields)

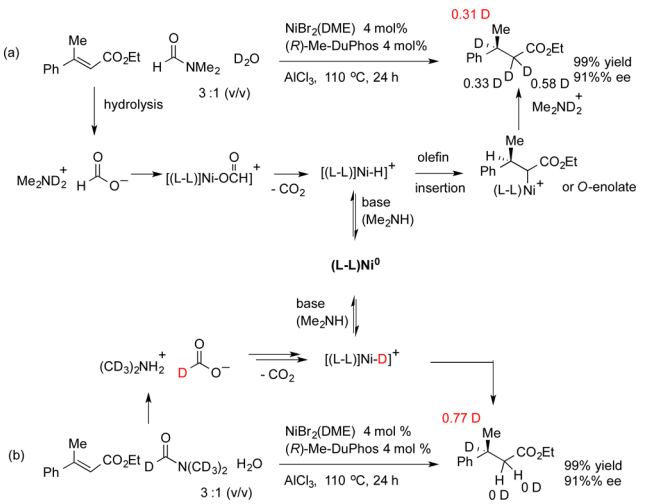


unfortunately. Thus, the β-aryl rings also contributed to the stereodifferentiating process. In the hydrogenation of (*E*)-phenylsuccinate, we obtained the product **2p** in 95% ee after the ancillary ligand was switched to TangPhos. When we changed the ester group of **1a** to other electron-withdrawing groups such as aldehyde, ketone, and amide, only partial conversion and moderate ee values were seen, for example, 40% conversion and 78% ee for the methyl ketone after 12 h at 110 °C. We found that aryl nitriles and nitro groups were reduced to a complex mixture. Moreover, simple aryl olefins did not react.

DMF was known to undergo acidic hydrolysis to give rise to *N*,*N*-dimethylammonium formate under heating.[17] When we heated a 3:1 mixture of DMF-d_7 (99.5% D) and D_2O (99.9% D) in the presence of $AlCl_3$ at 110 °C for 12 h, a small percentage of the formyl signal of DMF (8.18 ppm) was converted to a distinct signal at 8.49 ppm by proton NMR spectroscopy, which corresponded to the formate ion (signal for formic acid: 8.40 ppm).

When we used a mixture of DMF and D_2O in the model reaction (Scheme 3a), the product was deuterated at both α

Scheme 3. Deuterium-Labeling Experiments



positions with combined 0.91 D. This is expected from non-stereoselective α deuteration of the key nickel enolate[18] produced via asymmetric hydride insertion.[19] No deuteration of starting material was detected under the same conditions. The product also contained 0.31 D at the β position, probably caused by a parasitic equilibrium between the nickel hydride/deuteride and nickel(0) complexes. In another experiment using DMF-d_7 and H_2O, only the β position was labeled with 0.77 D (Scheme 3b).

In summary, we report an asymmetric-transfer hydrogenation of α,β-unsaturated esters using nickel catalysts and DMF as the hydride source. DMF decomposed in the presence of water and $AlCl_3$ to give the formate ion. In a recent calculation, we compared pathways of cationic hydridonickel(II) and neutral hydridonickel(I) complexes in asymmetric-transfer hydrogenation of ketimines.[10] The latter was found to have an exceedingly high barrier for the decarboxylation of formate to generate metal hydride species.

DOI: 10.1021/acs.orglett.6b02662
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02662.

Experimental procedures (PDF)
Spectral data for all new compounds (^{1}H and ^{13}C NMR, MS) (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank 2013 Singapore GSK-EDB Green and Sustainable Manufacturing Award and Nanyang Technological University for financial support.

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