Communication

Nickel-Catalyzed Desymmetric Hydrogenation of Cyclohexadienones: An Efficient Approach to All-Carbon Quaternary Stereocenters

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Nickel-Catalyzed Desymmetric Hydrogenation of Cyclohexadienones: An Efficient Approach to All-Carbon Quaternary Stereocenters

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ABSTRACT: The nickel-catalyzed desymmetric hydrogenation has been achieved. With the $Ni(OTf)_2$/(*S*,*S*)-Ph-BPE system, a series of γ,γ-disubstituted cyclohexadienones were transformed to the corresponding cyclohexenones with a chiral all-carbon quaternary center at the γ position in high yields (92% to 98%) and excellent enantioselectivities (92% to 99% ee). This catalytic system can also tolerate the desymmetric reaction of spirocarbocyclic cyclohexadienones to produce the corresponding cyclohexenones bearing a chiral spiro quaternary carbon with high yields (94% to 98%) and ee values (96% to 99% ee). Furthermore, this methodology provides an efficient and concise synthetic route to the intermediate of natural products cannabispirenones A and B.

All-carbon chiral quaternary stereocenters are important structural motifs in natural products and biologically active compounds (Figure 1a), while the construction of enantio-enriched all-carbon quaternary centers remains a significant challenge in chemical synthesis. In past decades, tremendous attention has been devoted to the stereocontrolled construction of all-carbon quaternary stereocentres using chemical catalysis, and many distinct catalytic enantioselective approaches have been established.[1] Among these methods, catalytic enantioselective desymmetrization of prochiral compounds or meso-compounds provides an efficient and attractive strategy in the construction of all-carbon quaternary stereocenters.[2,3] However, the desymmetric strategy in transition-metal (TM) catalyzed hydrogenation has far less developed[4] compared to direct enantioselective synthesis enabled by TM-catalyzed asymmetric hydrogenation.[5] Herein, we attempted to accomplish an approach to all-carbon quaternary stereocenters with high enantioselectivity by nickel-catalyzed desymmetric hydrogenation (Figure 1b).

In the past decades, asymmetric hydrogenation relying on precious metal compounds based on Rh, Ru, Ir, and Pd, etc. have been proven as a powerful synthetic method, which can be used in the preparation of many pharmaceuticals and biologically active molecules.[5] However, these second and third row transition metal compounds are very expensive and their reserves in the Earth's crust are declining. In contrast, catalysts containing first-row transition elements offer potential advantages in asymmetric catalysis as they are inexpensive, environmentally friendly and abundant. Recently, replacing the precious metals with earth-abundant transition metals such as manganese,[6] iron,[7] cobalt[8] and copper[9] has attracted a great deal of attention in the area of asymmetric hydrogenation and asymmetric transfer hydrogenation. Particularly, excellent results have been also obtained in the Ni-catalyzed asymmetric (transfer) hydrogenation of ketones,[10] alkenes[11] and imines.[12] However, to the best of our knowledge, the asymmetric hydrogenation of α,β-unsaturated ketones has been never tested in Ni-catalyzed system. Moreover, the desymmetric strategy in the first row TM-catalyzed asymmetric hydrogenation is still rare. Herein, for the first time, we report the nickel-catalyzed desymmetric hydrogenation to form the chiral quaternary stereocenters. Using cyclohexadienones as the substrates, a series compounds containing all-carbon quaternary stereocenters can be constructed in high yields (up to 98%) with excellent chemoselectivity and enantioselectivities (up to 99% ee).

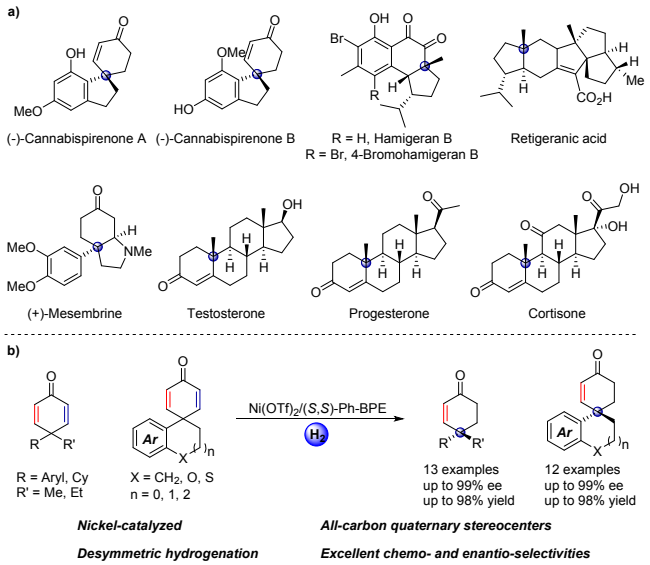
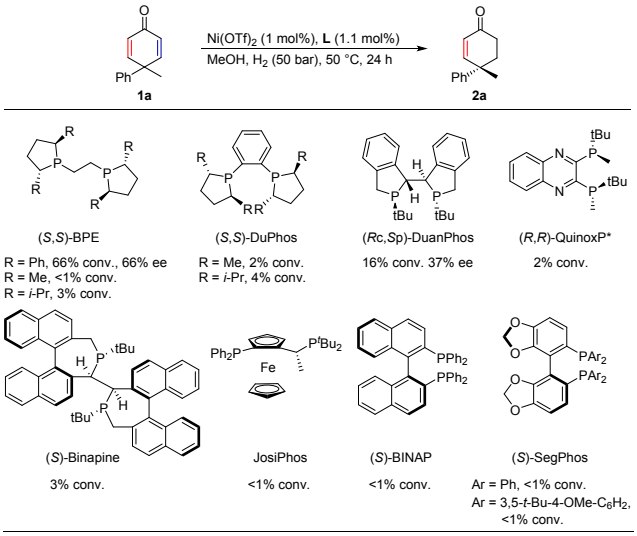


Figure 1. (a) Examples of natural products and biologically active compounds containing all-carbon quaternary stereocenters. (b) Ni-catalyzed desymmetric hydrogenation of cyclohexadienones.

We began the initial investigations with the desymmetric hydrogenation of **1a** to optimize the reaction conditions. A variety of chiral diphosphine ligands combined with $Ni(OTf)_2$ were examined for the hydrogenation of **1a** in methanol solution at 50 bar of H_2 at 50 °C (scheme 1). The evaluation of ligands revealed (*S*,*S*)-Ph-BPE to be superior to all others tested, although moderate conversion with moderate enantioselectivity was obtained. The use of (*Rc*,*Sp*)-DuanPhos as ligand afforded 16% conversion with only 37% ee. Ni catalysts based on other ligands, including Me-BPE, *i*-Pr-BPE, Me-DuPhos, *i*-Pr-DuPhos, QunioxP*, Binapine, JosiPhos, BINAP, SegPhos and DTBM-Segphos exhibited almost no activity for this reaction.

With the preliminary results in hand, we sought to obtain optimal reaction conditions, as summarized in Table 1. First, the mixture of MeOH with a series of other solvents (v/v = 1/9) were screened. When EtOH, iPrOH and EtOAc were used, >90% conversions were achieved and 74% to 79% ee values were obtained. In contrast, there was only <10% (even trace) conversion

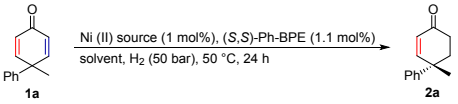
Scheme 1. Ligand Screening for the Ni-Catalyzed Desymmetric Hydrogenation of 1a[a]



[a]All reactions were carried out with a $Ni(OTf)_2$/ligand/substrate ratio of 1:1.1:100, in 1 mL of methanol, at 50 °C, under hydrogen (50 bar) for 24 h. Conversions were determined by ^1H NMR spectroscopy. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase.

when MeCN, THF, 1,4-dioxane and DCE were employed. Then, two nonpolar solvents, cyclohexane and toluene, were investigated. To our delight, full conversions with 87% ee (MeOH/cyclohexane = 1/9) and 89% ee (MeOH/toluene = 1/9) were obtained. When the reaction was carried out in toluene without MeOH, 93% ee was achieved but the conversion dropped to 52%, which indicated that the addition of MeOH can promote this transformation. Using a mixture of MeOH/toluene in a 1/19 ratio, 93% ee was given and complete conversion was afforded at the same time. In the meanwhile, other nickel precursors such as $NiCl_2$, $Ni(OAc)_2$ and $Ni(OAc)_2{\cdot}4H_2O$ were also tested. Other nickel(II) precursors than $Ni(OTf)_2$ resulted in eroded yield and ee value. It should be pointed out that no over-reduced products were detected and that **2a** was the only product in this conditions (50 °C, 50 bar H_2). If harsher conditions were applied, although higher ee values (97% ee) were obtained, which is in accordance with the Horeau principle[13], 9% over-reduced product (4-methyl-4-phenylcyclohexan-1-one) was observed (Table 1, entry 16).

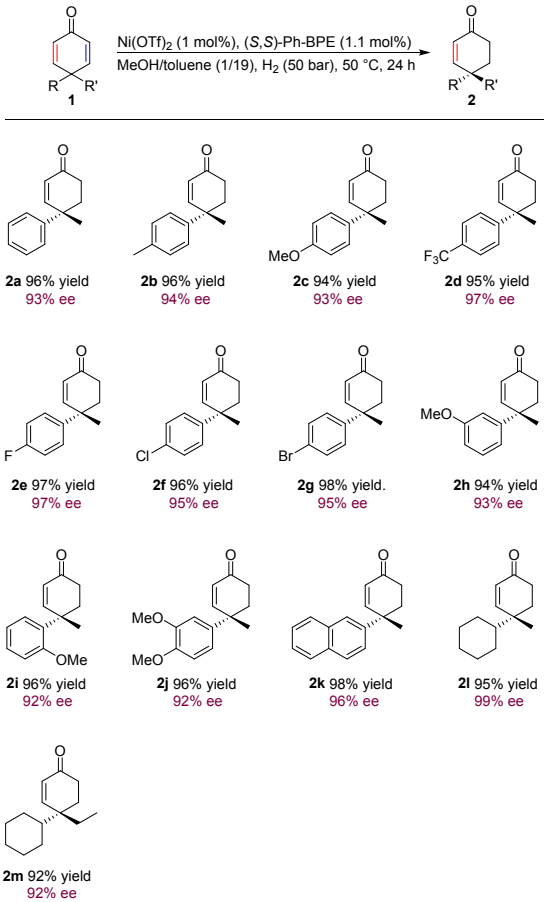
Table 1. Optimization of Reaction Conditions in the Ni-Catalyzed Desymmetric Hydrogenation of 1a[a]



entry	Ni (II)	solvent	conv. (%)[b]	ee (%)[c]
1	$Ni(OTf)_2$	MeOH	66	66
2	$Ni(OTf)_2$	EtOH	>99	74
3	$Ni(OTf)_2$	iPrOH	92	79
4	$Ni(OTf)_2$	EtOAc	94	78
5	$Ni(OTf)_2$	MeCN	3	-
6	$Ni(OTf)_2$	THF	9	-
7	$Ni(OTf)_2$	dioxane	<1	-
8	$Ni(OTf)_2$	DCE	4	-
9	$Ni(OTf)_2$	cyclohexane	>99	87
10[d]	$Ni(OTf)_2$	toluene	52	89
11[e]	**$Ni(OTf)_2$**	**toluene**	**>99**	**93**
12[e]	$NiCl_2$	toluene	<1	-
13[e]	$Ni(OAc)_2$	toluene	3	-
14[e]	$Ni(OAc)_2{\cdot}4H_2O$	toluene	<1	-
15[e]	$Ni(BF_4)_2{\cdot}6H_2O$	toluene	34	91
16[f]	$Ni(OTf)_2$	toluene	>99	97

[a] Unless otherwise mentioned, all reactions were carried out with a $Ni(OTf)_2$/(*S*,*S*)-Ph-BPE/substrate ratio of 1:1.1:100, in the mixture of MeOH (0.1 mL) with a series of other solvents (0.9 mL), at 50 °C, under hydrogen (50 bar) for 24 h. [b]Conversions were determined by ^1H NMR spectroscopy. [c]Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase. [d]The reaction was carried out in toluene without MeOH. [e]The reaction was carried out in the mixture of MeOH (0.05 mL) and toluene (0.95 mL). [f] 70 °C, H_2 (60 bar), the over-reduced product (4-methyl-4-phenylcyclohexan-1-one, 9%) was detected.

Scheme 2. Ni-Catalyzed Desymmetric Hydrogenation of Cyclohexadienones[a]

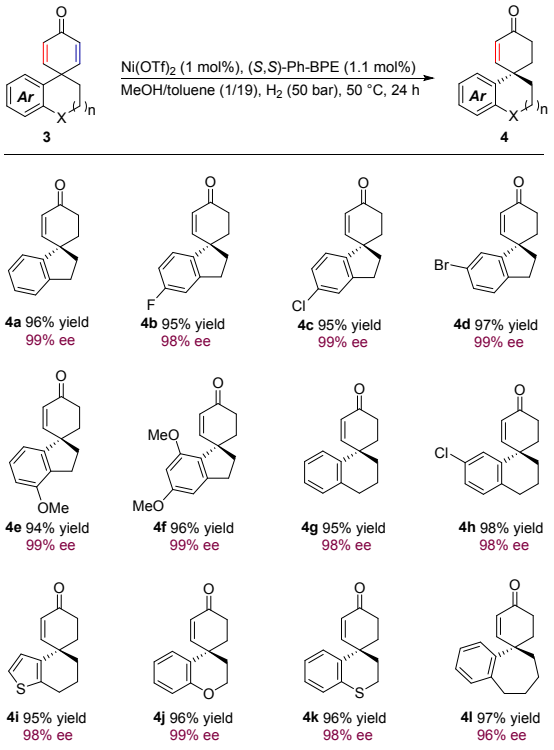


[a] Unless otherwise mentioned, all reactions were carried out with a $Ni(OTf)_2$/(*S*,*S*)-Ph-BPE/substrate ratio of 1:1.1:100, in the mixture of MeOH (0.05 mL) and toluene (0.95 mL), at 50 °C, under hydrogen (50 bar) for 24 h. Yield of the isolated product. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase.

With the optimized conditions in hand, we investigated the substrate scope and generality of this desymmetric transformation (Scheme 2). Many functional groups, such as methyl (**2b**), methoxyl (**2c**), trifluoromethyl (**2d**), and halides (**2e-2g**), at the para position of the phenyl group are compatible with this transformation. Substrates with *meta*- or *ortho*-substitution on the phenyl group are also tolerated, and excellent ee values were

obtained (**2h** and **2i**). Moreover, the product **2j** with disubstituted groups was obtained with high ee values as well. Reactions with 2-naphthyl-containing substrates proceeded smoothly, and **2k** was achieved in high yield with excellent enantioselectivity. Next, cyclohexadienones with two alkyl substituents were tested. When the aryl substituent was changed to a cyclohexyl group, the product **2l** was produced with 99% ee and 95% yield. Finally, the reaction of **1m**, with two different alkyl groups (cyclohexyl and ethyl), gave product **2m** with excellent enantioselectivity (92% ee).

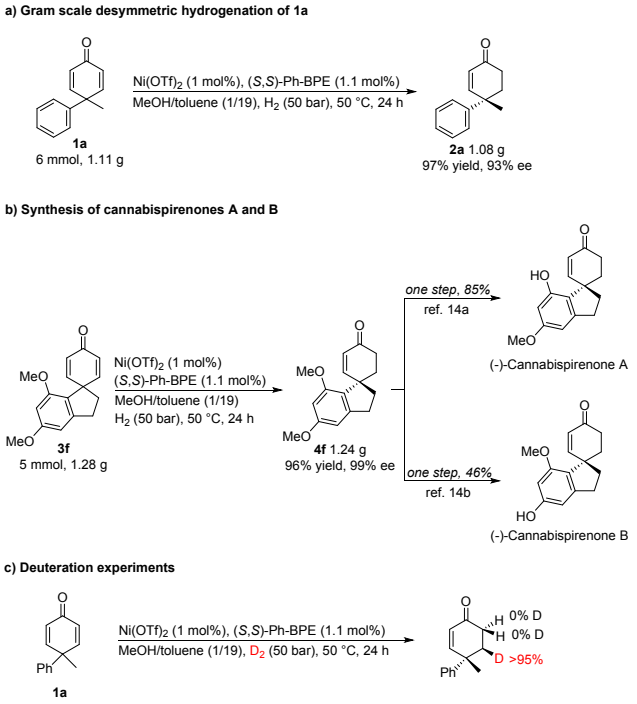
Scheme 3. Ni-Catalyzed Desymmetric Hydrogenation of Spirocyclic Cyclohexadienones[a]



[a] Unless otherwise mentioned, all reactions were carried out with a $Ni(OTf)_2$/(*S*,*S*)-Ph-BPE/substrate ratio of 1:1.1:100, in the mixture of MeOH (0.05 mL) and toluene (0.95 mL), at 50 °C, under hydrogen (50 bar) for 24 h. Yield of the isolated product. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase.

As spiro scaffolds bearing a chiral spiro quaternary carbon are widely present in natural products,[14] which exhibit biological and pharmacological activities, we investigated a series of cyclohexadienones incorporating a spirocarbocyclic backbone in current desymmetric reaction as well (Scheme 3). First, we used cyclohexadienone **3a** as the substrate, to our delight, the reaction proceeded smoothly under standard conditions and **4a** was obtained in high yield with excellent ee values (99% ee). Reactions of **3b-g**, with electrondonating or -withdrawing substituents at various positions of the aromatic ring gave the desired products in high yield with 98% to 99% ee. To explore the impact of the ring size of **3** on current desymmetric reaction, the transformation of **3** containing a six-membered ring was tested. The high yields (95%-98%) and excellent ee values (98% ee) of **4g-4i** illustrated these six-membered ring-containing substrates can be tolerated very well in current system. The spiro-fused heterocyclic compounds **3j** and **3k** are also accommodated, producing the desired products **4j** and **4k** in excellent yields and ee values. Furthermore, high enantioselectivity (96% ee) was observed for the reaction of **3l**, with a seven-membered ring, which demonstrated the strong tolerance of this desymmetric reaction.

Scheme 4. Transformations and Deuterium Labeling Studies



To demonstrate the synthetic utility of this desymmetric methodology, two gram-scale transformations were conducted, as summarized in scheme 4. First, under the standard reaction conditions, gram-scale **1a** was converted to the desired product **2a** in 97% yield with 93% ee. Then, the desymmetric reaction of **3f** was also conducted on a gram scale, and **4f** was obtained in 96% yield with undiminished enantioselectivity (99% ee). Notably, the chiral compound **4f** can be transformed to the natural products (-)-cannabispirenones A and B in just one step according to the reported procedure.[15] The deuterium labeling experiment was also conducted, and the results identified the role of methanol as a proton source to complete product, which is in agreement with the previous studies.[11b,c] Isotope labeling experiments supported a hypothesis that the reactive nickel hydride complex reacts with this conjugate enone in a 1,4-addition pathway, yielding an enolate which deprotonates methanol to form the product ketone. This outer-sphere manner is different from traditional inner-sphere mechanism which involves coordination of C=C bonds.

In conclusion, we have developed the Ni-catalyzed desymmetric hydrogenation of γ,γ-disubstituted cyclohexadienones. This method provides an efficient and concise route to the synthesis of compounds bearing a chiral all-carbon quaternary stereocenters, which are important intermediates in organic synthesis. Further investigation on the earth-abundant transition metal-catalyzed asymmetric hydrogenation is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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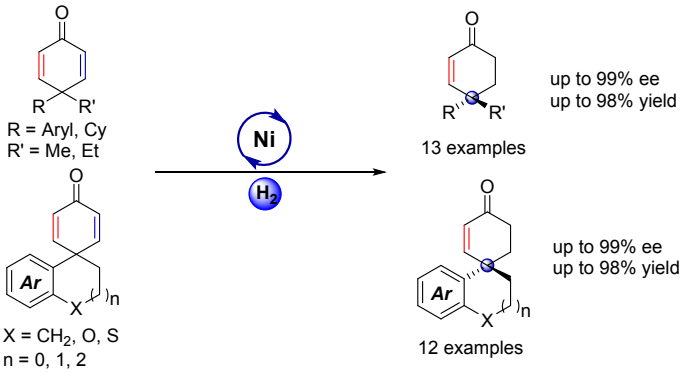
TOC Graphic:



Nickel-catalyzed Desymmetric hydrogenation

All-carbon quaternary stereocenters Excellent chemo- and enantio-selectivities