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Asymmetric Hydrogenation of β-Aryloxy/Alkoxy Cinnamic Nitriles and Esters

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Supporting Information

ABSTRACT: A highly efficient and enantioselective hydrogenation of β-aryloxy/alkoxy cinnamic nitriles and esters under mild conditions has been realized by using a rhodium catalyst with a chiral f-spiroPhos ligand. The method provides efficient access to the asymmetric synthesis of a variety of chiral β-oxy-functionalized nitriles and esters with excellent enantioselectivities (up to 99.9% ee) and high turnover numbers (TON of up to 50000). This methodology has also been successfully applied to the concise and practical synthesis of the chiral pharmaceutical nisoxetine.

Optically active β-oxy-functionalized nitriles are extremely important building blocks for the synthesis of a broad range of natural products, pharmaceuticals, and biologically active compounds,[1−3] such as fluoxetine, atomoxetine, nisoxetine, and duloxetine, which have attracted considerable attention as selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitor (SSRIs) for the treatment of depression-related disorders (Figure 1). In addition, these

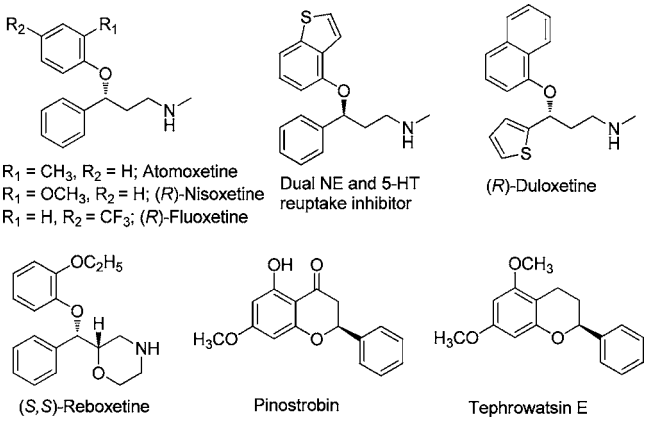
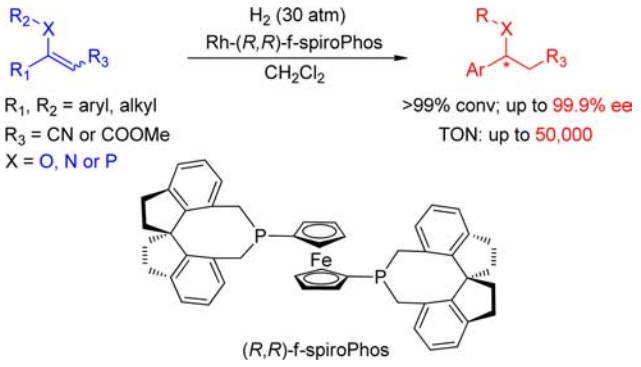


Figure 1. Representative pharmaceuticals, biologically active compounds, and natural products derived from chiral β-oxy-functionalized propanenitriles.

chiral nitriles can be readily converted to the corresponding other functional groups including amines, aldehydes, and carboxylic acids as well as their derivatives,[4] which are also very important synthetic intermediates for many biologically active compounds and pharmaceuticals.[5]

Because of their significance in chemical synthesis, great efforts have been devoted to the development of efficient approaches to chiral β-oxy-functionalized nitriles.[6] To the best of our knowledge, however, as one of the most atom-economic, environmentally friendly, and efficient methods for the synthesis of chiral β-oxy-functionalized nitriles, asymmetric hydrogenation of β-aryloxy or alkoxy cinnamic nitriles has not been explored so far despite the fact that some exciting results of asymmetric hydrogenation of vinyl ethers,[7] unsaturated nitriles,[8] and α- or β-aryloxy/alkoxy acrylic acids including their corresponding esters have been successfully reported.[9] Consequently, development of highly efficient catalysts for the asymmetric hydrogenation of β-aryloxy or alkoxy cinnamic nitriles is still very desirable and of significant importance in asymmetric synthesis. Herein, we report the first highly efficient asymmetric hydrogenation of β-aryloxy or alkoxy cinnamic nitriles and esters providing β-oxy-functionalized nitriles and esters with excellent enantioselectivities (up to 99.9% ee) and extremely high turnover numbers (TON of up to 50000) (Scheme 1).

Scheme 1. Rh-Catalyzed Asymmetric Hydrogenation of β-Aryloxy/Alkoxy Cinnamic Nitriles and Esters



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Our initial investigation began with the hydrogenation of (*Z*)-*β*-phenoxy cinnamic nitrile **1a** as the model substrate under 100 atm of H_2 in CH_2Cl_2 at room temperature with a variety of rhodium catalysts generated in situ from 0.5 mol % of $[Rh(COD)Cl]_2$ and a series of 2.2 mol % phosphorus ligands. A screening of chiral phosphorus ligands (Figure 2) available in

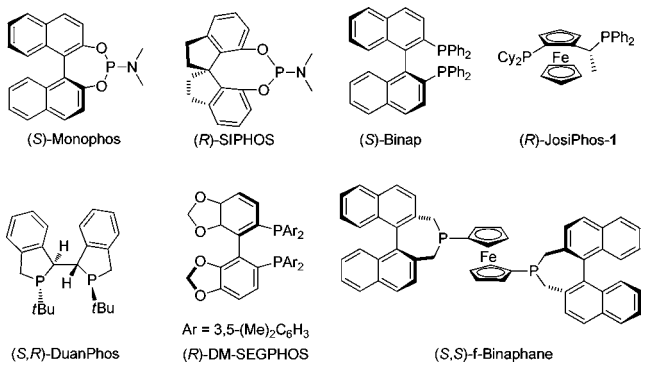
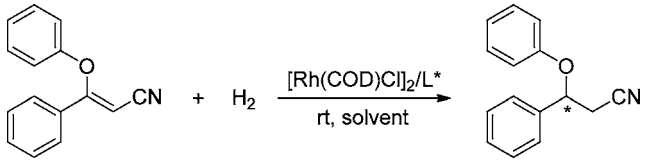


Figure 2. Structures of phosphine ligands evaluated in the hydrogenation of (*Z*)-*β*-phenoxy cinnamic nitrile **1a**.

our laboratory revealed that most of ligands including (*S*)-Monophos,[10] (*R*)-SIPHOS,[11] (*S*)-Binap,[12] (*R*)-DM-SEGPHOS,[13] and (*S*,*R*)-DuanPhos[14] exhibited poor activities and enantioselectivities (Table 1, entries 1−5), while (*R*)-JosiPhos-1[15] and (*S*,*S*)-f-Binaphane[16] also gave good enantioselectivities (93% ee and 90% ee, respectively) but with incomplete conversions (entries 6 and 7). Gratifyingly, (*R*,*R*)-f-spiroPhos[17] was most promising, achieving an excellent enantioselectivity of 99.9% ee with full conversion (entry 8). Subsequently, the solvent effect was investigated. In addition to CH_2Cl_2, THF, toluene, and DME were suitable for this hydrogenation and full conversions with comparable enantioselectivities were afforded (entries 9−11). However, use of 1,4-dioxane or MeOH as solvent gave incomplete conversions albeit with similar enantioselectivities (entries 12 and 13). To our delight, even under a lower H_2 pressure (30 atm) and in much shorter reaction time (1 h), the substrate **1a** could still be hydrogenated completely, providing the product **2a** with maintained enantioselectivity (entry 14).

A variety of *β*-aryloxy and alkoxy cinnamic nitriles **1b**−**p** were then readily prepared in high yields according to the method in Scheme 2[18] and hydrogenated using the Rh/f-spiroPhos catalyst under the optimized conditions. Regardless of the electronic property or position of the substituents in the aryloxy moiety of (*Z*)-*β*-aryloxy cinnamic nitriles (Scheme 3, **1a**−**h**), no apparent influence on enantioselectivities was observed, and hydrogenation products **2a**−**h** were obtained

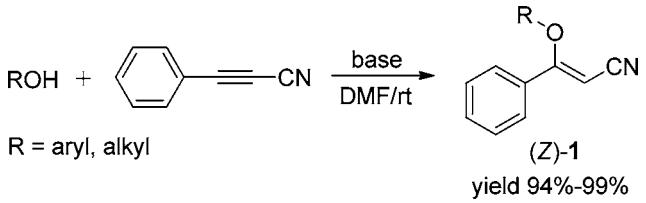
Table 1. Rh-Catalyzed Asymmetric Hydrogenation of 1a, Optimizing Reaction Conditions[a]



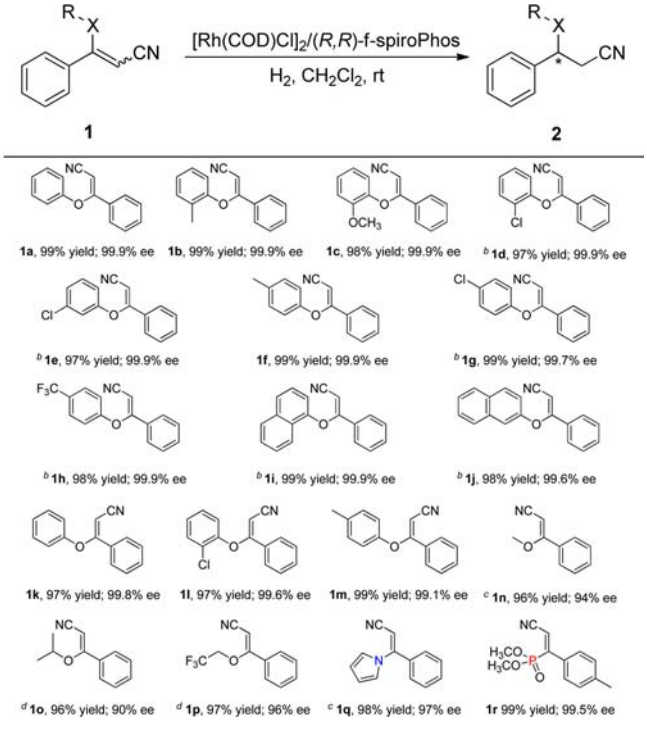
entry	ligand	solvent	conv[b] (%)	ee[c] (%)
1	(*S*)-Monophos	CH_2Cl_2	<5	ND
2	(*R*)-SIPHOS	CH_2Cl_2	<5	ND
3	(*S*)-Binap	CH_2Cl_2	<5	ND
4	(*R*)-DM-SEGPHOS	CH_2Cl_2	12	65
5	(*S*,*R*)-DuanPhos	CH_2Cl_2	10	42
6	(*R*)-JosiPhos-1	CH_2Cl_2	95	93
7	(*S*,*S*)-f-Binaphane	CH_2Cl_2	38	90
8	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	>99	99.9
9	(*R*,*R*)-f-spiroPhos	toluene	>99	97
10	(*R*,*R*)-f-spiroPhos	THF	>99	99
11	(*R*,*R*)-f-spiroPhos	DME	>99	98
12	(*R*,*R*)-f-spiroPhos	dioxane	95	99
13	(*R*,*R*)-f-spiroPhos	MeOH	87	98
14[d]	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	>99	99.9

[a]Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)Cl]_2$/phosphorus/substrate ratio of 0.5:2.2:100, 100 atm H_2, rt, 10 h. [b]Determined by ^1H NMR. [c]Determined by HPLC analysis using a chiral stationary phase. [d]30 atm of H_2, rt, 1 h.

Scheme 2. Synthesis of *β*-Aryloxy/Alkoxy Cinnamic Nitriles 1



Scheme 3. Substrate Scope of Rh-Catalyzed Asymmetric Hydrogenation of *β*-Aryloxy/Alkoxy Cinnamic Nitriles 1[a]



[a]Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)Cl]_2$/(*R*,*R*)-f-spiroPhos/substrate ratio of 0.5:1.1:100, 30 atm of H_2, rt, 1 h. The enantioselectivity was determined by HPLC or GC analysis using a chiral stationary phase. [b]50 atm of H_2, rt, 3 h. [c]50 atm of H_2, rt, 7 h. [d]50 atm of H_2, 50 °C, 36 h.

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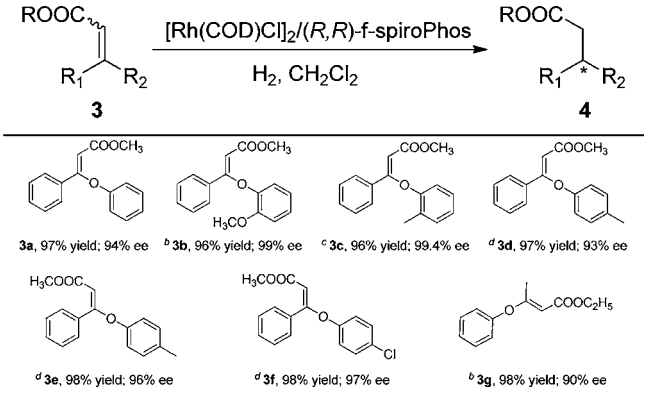
with excellent ee values. Substrates bearing both electron-donating substituents, such as Me or MeO groups, and electron-withdrawing substituents including Cl or CF_3 groups were smoothly hydrogenated with uniformly excellent enantioselectivities (**2a−h**, >99.7% ee). Both the 1-naphthyl and 2-naphthyl substrates (**1i** and **1j**) provided the desired products in excellent enantioselectivities, 99.9% ee and 99.6% ee, respectively. It is noteworthy that under identical conditions (*E*)-*β*-aryloxy cinnamic nitriles (**1k−m**) could also be successfully hydrogenated to afford the corresponding chiral products with a reversal of the absolute configuration contrast to those of the corresponding (*Z*)-isomers (**1a,d,f**) and comparable enantioselectivity, 99.8% ee, 99.6% ee, and 99.1% ee, respectively. However, the mixture of two isomers **1f** and **1m** (*Z*/*E* = 48:52) was hydrogenated with only 6% ee. It revealed that the *Z*/*E* ratio of substrates had an obvious effect on the enantioslectivity and the hydrogenation of (*Z*)- and (*E*)-isomers, affording products with opposite configuration and resulting in the dramatically decreased ee value. Besides substrates bearing aryloxyl groups, *β*-alkoxy cinnamic nitriles could be hydrogenated in high yields albeit with a little lower enantioselectivities. Substrates containing an alkoxyl group, such as MeO, ^{i}PrO, and CF_3CH_2O, were completely converted to the desired products with high enantioselectivities, 90−97% ee. Notably, the substrates bearing *N* or *P* heteroatoms, **1q** and **1r**, could also be hydrogenated to the chiral amine and phosphate with full conversions and excellent enantioselectivities (97% ee and 99.5% ee, respectively), which could be used as chiral auxiliaries, resolving reagents and building blocks for synthesis of a variety of natural products, pharmaceuticals, and biologically active compounds.[19]

Furthermore, to our delight, this catalyst system also exhibited very high enantioselectivity in the asymmetric hydrogenation of *β*-aryloxy cinnamic esters (Scheme 4), which was not reported until now. Adjusting some reaction conditions, a series of *β*-aryloxy cinnamic esters **3** were successfully hydrogenated giving chiral esters **4** with high ee values of over 90%. Much higher enantioselectivities (up to 99.4% ee) were provided in the hydrogenation of substrates **3b** and **3c** bearing an *ortho* substituent albeit with the requirements

Scheme 4. Substrate Scope of Rh-Catalyzed Asymmetric Hydrogenation of Various Substrates 3[a]

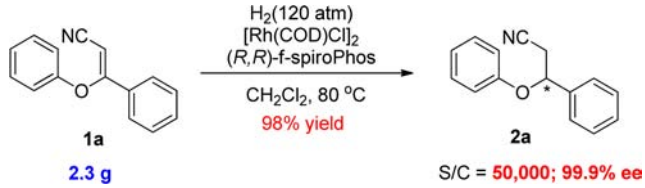


[a]Unless otherwise mentioned, all reactions were carried out with a [Rh(COD)Cl]$_2$/(*R*,*R*)-f-spiroPhos/substrate ratio of 0.5:1.1:100, 30 atm of H_2, rt, 3 h. The enantioselectivity was determined by HPLC analysis using a chiral stationary phase. [b]80 atm of H_2, 60 °C, 48 h. [c]80 atm of H_2, 60 °C, 72 h. [d]50 atm of H_2, rt, 12 h.

of higher hydrogen pressure and longer reaction time for achieving full conversions.

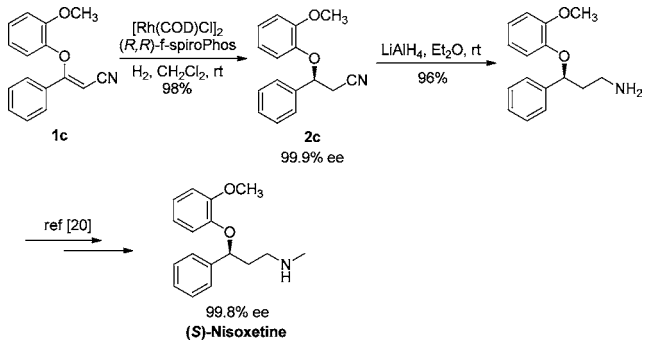
More remarkably, even on a gram scale and with an extremely lower catalyst loading as 0.002 mol % of the Rh-(*R*,*R*)-f-spiroPhos catalyst, the hydrogenation of the substrate **1a** could be successfully accomplished to provide the corresponding product **2a** in high yield, and the excellent enantioselectivity remained unchanged, 99.9% ee. These results indicated that this catalyst was exceptionally efficient for the asymmetric hydrogenation of this class of substrates and showed very high activity approaching 50000 of turnover numbers (TON) (Scheme 5).

Scheme 5. Asymmetric Hydrogenation of 1a under Lower Catalyst Loading



In addition, this catalyst system was also successfully applied to the synthesis of important chiral pharmacophore fragments. For example, the hydrogenation product **2c** obtained from the asymmetric hydrogenation of the substrate **1c** was further reduced to give *γ*-aryloxy amines, which could be readily converted to the chiral pharmaceutical nisoxetine in high yield with maintained enantioselectivity as high as 99.8% ee (Scheme 6).[20] This method provided an alternative to prepare some chiral pharmaceuticals and reuptake inhibitors such as fluoxetine, atomoxetine, nisoxetine, and duloxetine.

Scheme 6. Synthesis of Nisoxetine via Asymmetric Hydrogenation of 1c



In conclusion, a highly efficient and enantioselective hydrogenation of *β*-aryloxy/alkoxy cinnamic nitriles under mild conditions has been first realized by using a rhodium catalyst with a chiral f-spiroPhos ligand. The method provides an efficient access to the asymmetric synthesis of a variety of *β*-oxy-functionalized nitriles and esters with excellent enantioselectivities (up to 99.9% ee) and high turnover numbers (up to 50000). This methodology has also been successfully applied to the concise and practical synthesis of the chiral pharmaceutical nisoxetine and provides an alternative to asymmetric synthesis of some chiral pharmaceuticals such as fluoxetine, atomoxetine, and nisoxetine.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02393.

Experimental procedures, compound characterization data, and analysis of enantioselectivities of hydrogenation products (PDF)

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Notes

The authors declare no competing financial interest.

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