Highly Efficient Rh-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Nitriles

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Highly Efficient Rh-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Nitriles

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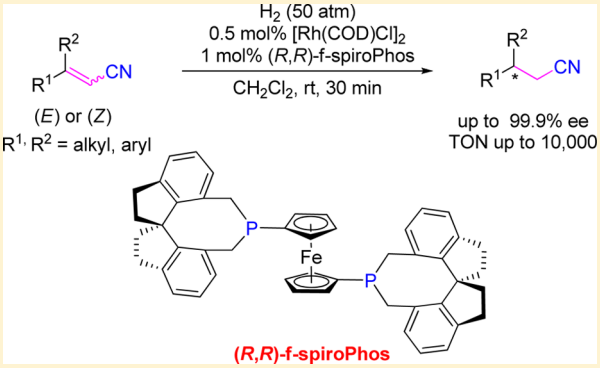
Supporting Information

ABSTRACT: A highly efficient enantioselective hydrogenation of α,β-unsaturated nitriles catalyzed by Rh-(*R*,*R*)-f-spiroPhos complex has been developed. With Rh-(*R*,*R*)-f-spiroPhos catalyst and under mild conditions, a wide range of α,β-unsaturated nitriles including the (*E*)- and (*Z*)-isomers of 3-alkyl-3-aryl, 3,3-diaryl, and 3,3-dialkyl α,β-unsaturated nitriles were hydrogenated to the corresponding chiral nitriles with excellent enantioselectivities (up to 99.9% ee) and high turnover numbers (TON up to 10,000).



1. INTRODUCTION

The chiral 3,3-disubstituted propionitriles are important synthetic intermediates for many biologically active compounds and pharmaceuticals, such as ar-turmerone,[1] florhydral,[2] Tolterodine,[3] indatraline,[4] and arpromidine[5] (Figure 1). In addition, these nitriles can be readily converted to other useful compounds, such as amines, aldehydes, and carboxylic acids. Due to their significance in chemical synthesis, the development of efficient enantioselective synthetic protocols has attracted considerable attentions. Among these, the metal-catalyzed conjugate reduction of α,β-unsaturated nitriles represents the predominant. However, presumably because of the intrinsic low reactivity of these substrates and the linearity of the nitrile group,[6,7a,8] which is not suitable for the assistant coordination between the C═C bond and metal catalyst, reports on efficient catalyst systems for the asymmetric reduction of α,β-unsaturated nitriles have been very limited so far. The Co-catalyzed conjugate reduction of these substrates with sodium borohydride provided saturated nitriles with only moderate enantioselectivities, up to 69% ee.[9] Higher enantioselectivities could be achieved using the copper-josiphos-catalyzed asymmetric hydrosilylation with polymethylhydrosiloxane (PMHS).[7] Although the catalytic asymmetric hydrogenation has been one of the most powerful approaches to chiral compounds and great progress has been made,[10] there are only a few examples involving asymmetric hydrogenation of α,β-unsaturated nitriles, and high enantioselectivities could only be achieved for the substrates with an assistant coordinating group such as an acetamido or carboxylate group attached to the C═C bond.[11] More recently, in combination with *N*,*N*-diisopropylethylamine (DIPEA), a Ir/N,P complex exhibited a high reactivity and enantioselectivity only for *E*-α,β-unsaturated nitriles, but poor conversions or enantioselectivities were observed for the corresponding *Z*-isomers.[8]

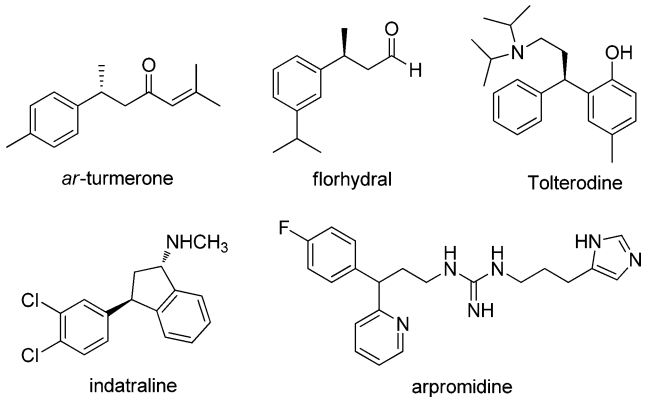


Figure 1. Key structural elements in chiral pharmaceuticals.

We have recently developed a new type of chiral diphosphine ligand f-spiroPhos based on privileged spirobiindane skeleton, developed by Zhou and co-workers,[12] and demonstrated its iridium complex was highly efficient for the hydrogenation of β-acylamino nitroolefins.[13] When we evaluated this chiral diphosphine ligand for the hydrogenation of α,β-unsaturated nitriles without any additional chelating groups, we fortunately found its rhodium complex showing excellent enantioselectivities (up to 99.9% ee) and high reactivities (TON up to 10,000) for a wide range of substrates including both *E*- and *Z*-isomers of 3-alkyl-3-aryl, 3,3-diaryl, and 3,3-dialkyl α,β-unsaturated nitriles under mild reaction conditions (Scheme 1).

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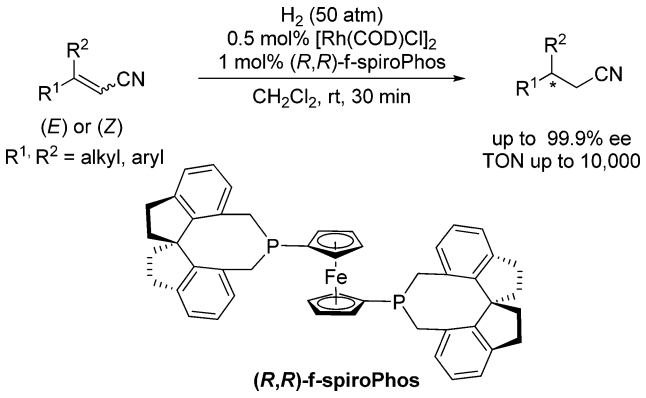
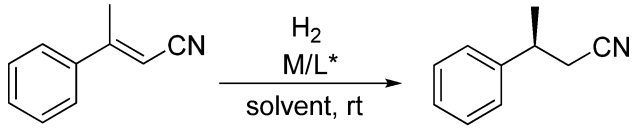
Scheme 1



2. RESULTS AND DISCUSSION

2.1. Asymmetric Hydrogenation of (*E*)-3-Alkyl-3-aryl *α,β*-Unsaturated Nitriles. Initially, (*E*)-3-phenylbut-2-enenitrile **1a** was used as the model substrate, and the hydrogenation was performed under 60 atm of H_2 in CH_2Cl_2 at room temperature using the complex of (*R,R*)-f-spiroPhos and $[Ir(COD)Cl]_2$, which was very efficient for the hydrogenation of nitroalkenes.[13] Despite full conversion, only moderate enantioselectivity was achieved, 64% ee (Table 1, entry 1). After investigation of the metal precursors, we found that $[Rh(COD)Cl]_2$ was the best choice and showed both high enantioselectivity and activity, 96% ee and complete conversion (entry 3). Furthermore, a brief screening of chiral phosphorus ligands available in our laboratory revealed that most of phosphorus ligands, including (*S*)-BINAP, (*S,R*)-DuanPhos, (*R*)-JosiPhos-1, (*S,S*)-f-Binaphane, and (*S*)-MonoPhos, gave either low conversions or poor enantioselectivities (up to 57% ee, entries 4−8). The effect of solvents was also explored. This hydrogenation could be performed smoothly with good enantioselectivities in most of solvents, such as THF, toluene, and DME (entries 10−12), but not in methanol (entry 9). In addition to CH_2Cl_2, dioxane is also suitable for the hydrogenation, and comparable results were observed (96% ee, entry 13). Interestingly, lower hydrogen pressures have a negative effect on the enantioseletivity of this reaction. Decreasing the hydrogen pressure from 60 to 5 atm led to a decrease in enantioselectivity (entries 14−15), while the conversion remains unchanged. Moreover, under 50 atm of H_2, this hydrogenation could be completed in 30 min with unchanged enantioselectivity (entry 16).

Table 1. Asymmetric Hydrogenation of (*E*)-3-Phenylbut-2-enenitrile, 1a, Optimizing Reaction Conditions[a]



1a **2a**

entry	ligand	solvent	conv. (%)[b]	ee (%)[c]
1[d]	(*R,R*)-f-spiroPhos	CH_2Cl_2	>99	64
2[e]	(*R,R*)-f-spiroPhos	CH_2Cl_2	61	58
3	(*R,R*)-f-spiroPhos	CH_2Cl_2	>99	96
4	(*S*)-BINAP	CH_2Cl_2	4	57
5	(*S,R*)-DuanPhos	CH_2Cl_2	6	24
6	(*R*)-JosiPhos-1	CH_2Cl_2	20	9
7	(*S,S*)-f-Binaphane	CH_2Cl_2	89	47
8	(*S*)-MonoPhos	CH_2Cl_2	0.9	14
9	(*R,R*)-f-spiroPhos	MeOH	94	31
10	(*R,R*)-f-spiroPhos	THF	>99	86
11	(*R,R*)-f-spiroPhos	toluene	>99	74
12	(*R,R*)-f-spiroPhos	DME	>99	93
13	(*R,R*)-f-spiroPhos	dioxane	>99	96
14[f]	(*R,R*)-f-spiroPhos	CH_2Cl_2	>99	91
15[g]	(*R,R*)-f-spiroPhos	CH_2Cl_2	>99	93
16[h]	(*R,R*)-f-spiroPhos	CH_2Cl_2	>99	96

[a]Reaction conditions: $[Rh(COD)Cl]_2$/phosphine/substrate ratio = 0.5:2.1:100, 60 atm H_2, 12 h, rt. [b]Determined by GC analysis. [c]Determined by chiral GC using a Supelco Alpha-Dex 225 column (30 m × 0.25 mm × 0.25 μm). [d]$[Ir(COD)Cl]_2$. [e]$[Rh(COD)_2]BF_4$. [f]5 atm H_2. [g]20 atm H_2. [h]50 atm H_2, 30 min.

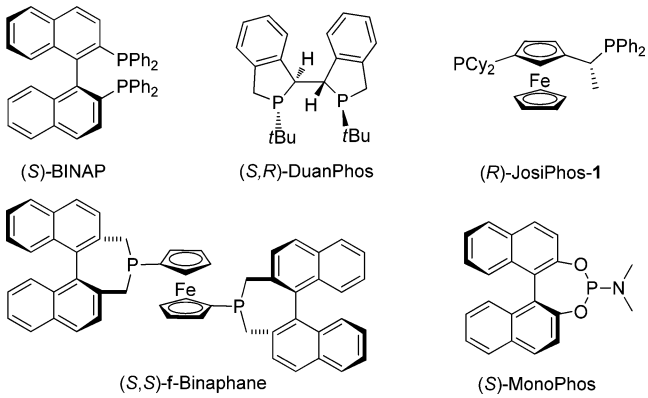


Figure 2. Structures of the phosphine ligands for hydrogenation of (*E*)-3-phenylbut-2-enenitrile **1a**.

Under the optimal reaction conditions a variety of (*E*)-3-alkyl-3-aryl *α,β*-unsaturated nitriles **1** were evaluated and provided the corresponding chiral nitriles with 95−99.7% ee (Table 2). The electron property and position of the substituents in the phenyl ring of the substrates had no obvious effect on both the reactivity and enantioseleltivity. Generally, the substrates with electron-withdrawing substituents on the phenyl ring gave relatively higher enantioselectivity than those with electron-donating substituents. For example, the substrate (*E*)-**1f** with a *para*-methyl group gave 95% ee (entry 6), while the substrates with a *para*-chloro ((*E*)-**1c**), bromo ((*E*)-**1d**), or nitro group ((*E*)-**1e**) yielded **2c**, **2d**, and **2e** with as high as 97% ee (enties 3−5). The substrates with substituents at *meta*- or *ortho*-position of the phenyl ring also gave higher enantioselelctivities than those with substituents at *para*-position, and the substrate (*E*)-**1l** provided product **2l** with the highest ee value of 99.7% (entry 12). The substrate (*E*)-**1q** with a heterocyclic pyridinyl ring also afforded the product **2q** with an excellent enantioselectivity (99% ee), but higher hydrogen pressure and longer reaction time were required to complete the reaction (entry 17). This reduced activity may be attributed to the strong inhibitory effect of the pyridinyl group on the catalyst. The substrates with a larger 3-alkyl substituent such as Et, ^{i}Pr, and C_5H_9 ((*E*)-**1r** to **1t**) also gave comparable or even better enantioselelctivity than that provided by the model substrate (*E*)-**1a** (entries 18−20).

Furthermore, it is notable that this catalyst system was also highly efficient for the hydrogenation of the (*Z*)-isomers of the substrates **3**, providing the corresponding products **4** with good

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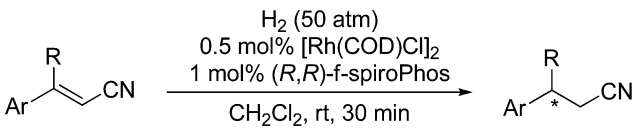
Table 2. Rh-Catalyzed Asymmetric Hydrogenation of (*E*)-3-Alkyl-3-aryl α,β-Unsaturated Nitriles[a]

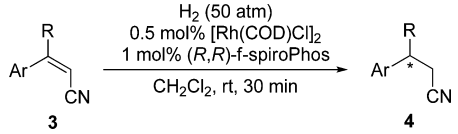


entry	Ar	R	product	conv. (%)[b]	ee (%)[c]
1	(*E*)-C_6H_5 (**1a**)	Me	**2a**	>99(98)	96(*S*)
2	(*E*)-4-FC_6H_4 (**1b**)	Me	**2b**	>99(98)	95(−)
3	(*E*)-4-ClC_6H_4 (**1c**)	Me	**2c**	>99(98)	97(+)
4	(*E*)-4-BrC_6H_4 (**1d**)	Me	**2d**	>99(97)	97(+)
5	(*E*)-4-$NO_2C_6H_4$ (**1e**)	Me	**2e**	>99(96)	97(+)
6	(*E*)-4-MeC_6H_4 (**1f**)	Me	**2f**	>99(98)	95(*S*)
7	(*E*)-3-ClC_6H_4 (**1g**)	Me	**2g**	>99(96)	97(+)
8	(*E*)-3-BrC_6H_4 (**1h**)	Me	**2h**	>99(97)	97(+)
9	(*E*)-3-$NO_2C_6H_4$ (**1i**)	Me	**2i**	>99(97)	98(−)
10	(*E*)-3-$MeOC_6H_4$ (**1j**)	Me	**2j**	>99(98)	98(−)
11	(*E*)-2-FC_6H_4 (**1k**)	Me	**2k**	>99(98)	96(−)
12	(*E*)-2-ClC_6H_4 (**1l**)	Me	**2l**	>99(98)	99.7(−)
13	(*E*)-2-MeC_6H_4 (**1m**)	Me	**2m**	>99(97)	99.5(−)
14	(*E*)-2-$NO_2C_6H_4$ (**1n**)	Me	**2n**	>99(96)	99(+)
15	(*E*)-1-naphthyl (**1o**)	Me	**2o**	>99(97)	98(−)
16	(*E*)-2-naphthyl (**1p**)	Me	**2p**	>99(98)	96(+)
17[d]	(*E*)-3-pyridinyl (**1q**)	Me	**2q**	>99(96)	99(−)
18	(*E*)-C_6H_5 (**1r**)	Et	**2r**	>99(95)	96(−)
19	(*E*)-C_6H_5 (**1s**)	^{i}Pr	**2s**	>99(98)	99(−)
20	(*E*)-C_6H_5 (**1t**)	C_5H_9	**2t**	>99(98)	98(−)

[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, CH_2Cl_2, 50 atm H_2, rt, 30 min. [b]Determined by ^{1}H NMR spectroscopy or GC analysis; data in parentheses are isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis. [d]80 atm H_2, 24 h.

to excellent enantioslectivities (89−97% ee) (Table 3). Although the enantioselectivities of the hydrogenation of (*Z*)-isomers were relatively lower than those obtained by the corresponding (*E*)-isomers and with opposite configuration,

Table 3. Rh-Catalyzed Asymmetric Hydrogenation of (*Z*)-3-Alkyl-3-aryl α,β-Unsaturated Nitriles[a]



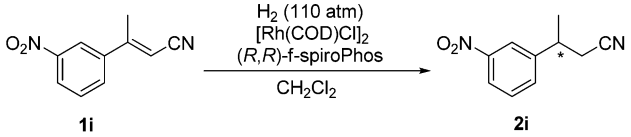
entry	Ar	R	product	conv (%)[b]	ee (%)[c]
1	(*Z*)-4-ClC_6H_4(**3a**)	Me	**4a**	>99(96)	89(−)
2	(*Z*)-2-FC_6H_4 (**3b**)	Me	**4b**	>99(95)	94(+)
3	(*Z*)-2-ClC_6H_4 (**3c**)	Me	**4c**	>99(97)	97(+)
4	(*Z*)-2-MeC_6H_4 (**3d**)	Me	**4d**	>99(96)	95(+)
5	(*Z*)-1-naphthyl (**3e**)	Me	**4e**	>99(95)	92(+)
6	(*Z*)-C_6H_5 (**3f**)	Et	**4f**	>99(95)	93(+)
7	(*Z*)-C_6H_5 (**3g**)	^{i}Pr	**4g**	>99(96)	97(+)

[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, CH_2Cl_2, 50 atm H_2, rt, 30 min. [b]Determined by ^{1}H NMR spectroscopy or GC analysis; data in parentheses are isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis.

this provided the first example of highly efficient asymmetric hydrogenation of both the (*E*)- and (*Z*)-isomers of α,β-unsaturated nitriles to produce either desired enantiomer, (*S*) or (*R*)-enantiomer of chiral nitriles with similar enantioselectivities.

Most importantly, this is a very highly efficient method for the synthesis of chiral nitriles. With Rh-(*R*,*R*)-f-spiroPhos catalyst and the hydrogenation of the easily obtained (*E*)-**1i** at a catalyst loading of 0.02 mol % under 110 atm of initial H_2 pressure at room temperature performed, **2i** was obtained in >99% conversion with 99.3% ee. Further deceasing the catalyst loading to 0.01 mol %, >99% conversion and 98% ee were also obtained under the same initial H_2 pressure at 40 °C (Scheme 2). This result indicated that Rh-(*R*,*R*)-f-spiroPhos was exceptional highly efficient for the hydrogenation of α,β-unsaturated nitriles and could provide TONs approaching 10,000.

Scheme 2



rt, S/C=5000, >99% conv. 99.3% ee
40 °C, S/C=10,000, >99% conv. 98% ee

2.2. Asymmetric Hydrogenation of (*E*)- and (*Z*)-3,3-Diarylacrylonitriles. Encouraged by the promising results obtained by the asymmetric hydrogenation of the (*E*)- and (*Z*)-isomers of 3-alkyl-3-aryl α,β-unsaturated nitriles **1** and **3**, we then studied the asymmetric hydrogenation of 3,3-diarylacrylonitriles with Rh-(*R*,*R*)-f-spiroPhos catalyst. To date, only a few catalysts showed high activity and good enantioselectivity for the hydrogenation of the unsaturated substrates bearing diaryl substituents at the C═C, C═O, or C═N bond.[14] To the best of our knowledge, no example for the asymmetric hydrogenation of 3,3-diarylacrylonitriles has been reported so far, and we found that the Rh-(*R*,*R*)-f-spiroPhos catalyst was also very highly efficient for this type of substrates.

Based on the optimal conditions for the hydrogenation of 3-alkyl-3-aryl α,β-unsaturated nitriles **1** and **3**, we found that by prolonging the reaction time from 0.5 to 6 h a wide range of (*E*)-3,3-diarylacrylonitriles could be hydrogenated to the corresponding products **6** in >99% conversions with 94−99.9% ee (Table 4). These results revealed that the electronics and the steric hindrance of substituents on the aryl groups had no obvious effect on the enantioselectivities. Remarkably, even for the hydrogenation of (*Z*)-3,3-diarylacrylonitriles, such as **5f** and **5o**, the catalyst system provides the desired products with excellent enantioselectivities, 96% and 99.7% ee, respectively, with a reversal of the absolute configuration. The performance of the new Rh-f-spiroPhos catalyst system in the asymmetric hydrogenation of 3,3-diarylacrylonitriles was also evaluated on a gram scale. Under optimized reaction conditions, substrate **5k** (1.0 g) was smoothly hydrogenated providing the corresponding product in excellent yield (99% isolated yield) almost without any loss of enantioselectivity, 99.4% ee.

2.3. Asymmetric Hydrogenation of 3,3-Dialkyl and 2-Alkyl-3-aryl α,β-Unsaturated Nitriles 7 and 9. In addition, the asymmetric hydrogenation of 3,3-dialkyl and 2-alkyl-3-aryl

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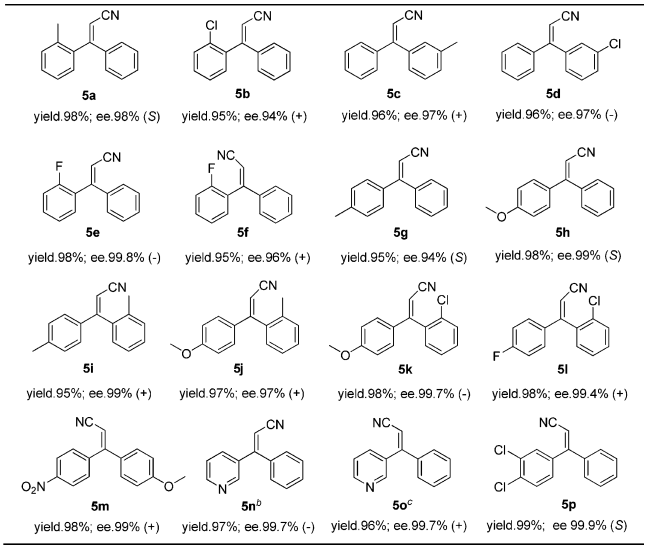
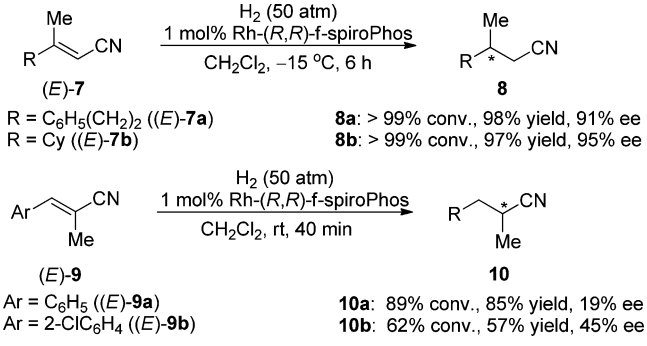
Table 4. Rh-Catalyzed Asymmetric Hydrogenation of 3,3-diarylacrylonitriles 5[a]



[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, CH_2Cl_2, 50 atm H_2, rt, 6 h. The conversion was determined by ^1H NMR spectroscopy; the enantioselectivity was determined by HPLC analysis using a chiral stationary. [b]40 °C, 12 h. [c]12 h.

α,β-unsaturated nitriles was also evaluated with Rh-(*R*,*R*)-f-spiroPhos catalyst (Scheme 3). Under the similar conditions for

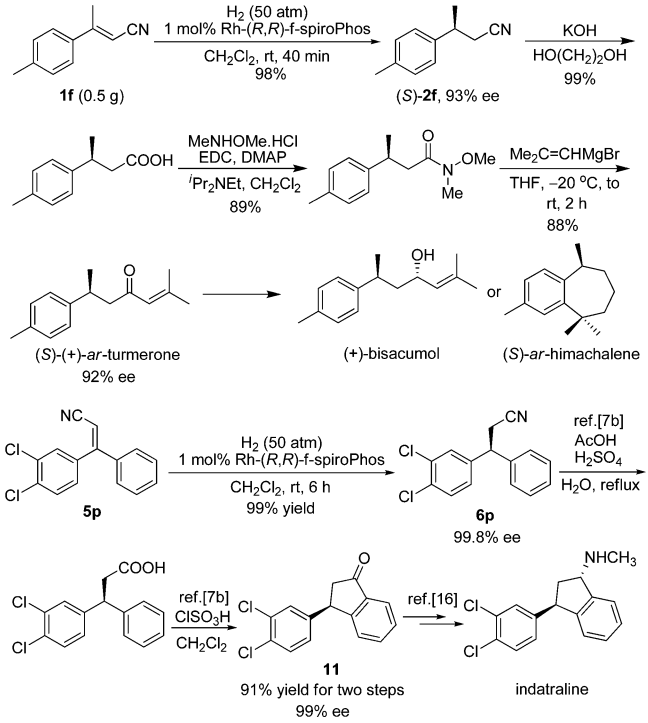
Scheme 3



the hydrogenation of **1** and **3**, (*E*)-3,3-dialkyl *α,β*-unsaturated nitriles **7a** and **7b** were hydrogenated to chiral nitriles **8a** and **8b** in full conversions with 91 and 95% ee, respectively, after reacted at −15 °C for 6 h. With a substituent group at the *α*-position of the *α,β*-unsaturated nitriles, the reaction became sluggish. The asymmetric hydrogenation of (*E*)-3-aryl-substituted methacrylonitriles **9a** and **9b** gave incomplete conversion with 19% and 45% ee, respectively.

2.4. Application of the Rh-(*R*,*R*)-f-spiroPhos Catalyst in the Synthesis of Biologically Active Compounds and Pharmaceuticals. Furthermore, this method was successfully applied to the enantioselective preparation of (*S*)-(+)-ar-turmerone as a spice flavor of turmeric in high yield and enantioselectivity. The produced (*S*)-(+)-ar-turmerone can be converted to (+)-bisacumol, which is usually isolated from the rhizome of *Curcuma xanthorrhiza* as a member of the aromatic bisabolane sesquiterpene family, and (*S*)-ar-himachalene, a pheromone component of the flea beetle.[15] The key intermediate **11** for the synthesis of indatraline, which is a potent psychoactive compound with high inhibitory activity for monoamine reuptake,[4] can also be readily prepared by this method from 3,3-diarylacrylonitrile **5p** in high yield with excellent enantioselectivity, 99% ee (Scheme 4). Importantly, this strategy is more efficient than others reported in the literature.[7b,16]

Scheme 4



According to the reported mechanism of rhodium- and iridium-catalyzed asymmetric hydrogenation reactions,[17] a plausible mechanism of this transformation and possible enantio-determining transition model was also proposed (Scheme 5). The ferrocenyl group of the ligand blocked one side of the complex and the substrate could only coordinate to rhodium from the other side. The enantio-determining transition model showed that the coordination of the (*E*)-substrate to rhodium was much more favorable from the *re*-face of the *α,β*-unsaturated nitriles, which led to the (*S*) products. For the (*Z*)-substrate, the coordination was more favorable from the *si*-face to afford the (*R*) products. These were in agreement with the stereochemical outcome of the hydrogenation products.

3. CONCLUSION

In conclusion, we have developed a highly efficient method for enantioselective hydrogenation of *α,β*-unsaturated nitriles to optical active saturated nitriles. With a rhodium complex bearing a spirobiindane-based chiral diphosphine (*R*,*R*)-f-spiroPhos ligand, a wide range of *α,β*-unsaturated nitriles including the (*E*)- and (*Z*)-isomers of 3-alkyl-3-aryl, 3,3-diaryl, and 3,3-dialkyl *α,β*-unsaturated nitriles were hydrogenated to the corresponding chiral nitriles with excellent enantioselectivities (up to 99.9% ee) and TONs (up to 10,000). Further studies are underway and will be reported in due course.

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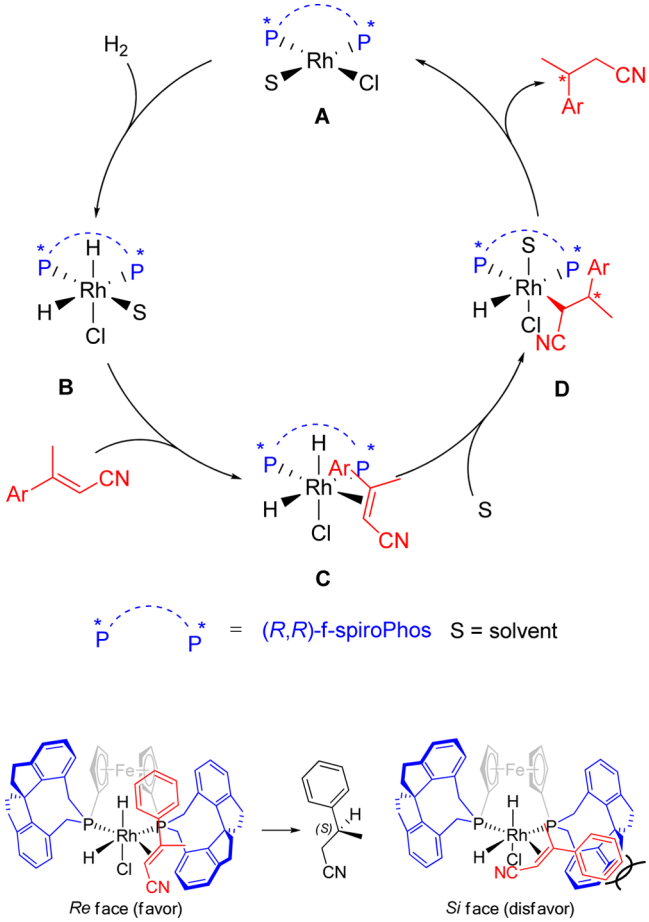
Scheme 5. Proposed Mechanism and Stereorecognition Model for Rh-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Nitriles



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06418.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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