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Pyridine-Directed Asymmetric Hydrogenation of 1,1-Diarylalkenes

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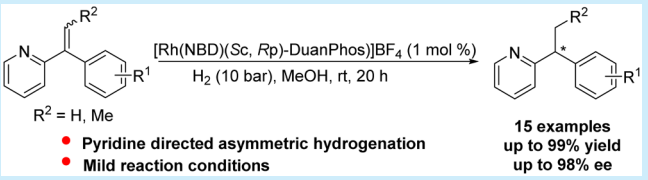
Supporting Information

ABSTRACT: Highly enantioselective pyridine-directed rhodium-catalyzed asymmetric hydrogenation of challenging 1,1-diarylalkenes is achieved by using [Rh(NBD)DuanPhos]BF_4 as a precatalyst. Various types of 2-pyridine substituted 1,1-diarylalkenes could be hydrogenated with good to excellent enantioselectivities, which provide an efficient route to the synthesis of pharmaceutically and biologically active compounds containing a 2-pyridyl ethane unit.



In recent decades, homogeneous asymmetric hydrogenation of alkenes has attracted great interest,[1] and transition metal-catalyzed asymmetric hydrogenation of multiple-substituted C=C bonds has become one of the most important methods to prepare enantiopure compounds because of its advantages of high efficiency and being environmentally friendly.[2] In this context, a variety of alkenes have been hydrogenated with excellent enantioselectivities.

However, there are only a few reports about asymmetric hydrogenation of 1,1-diarylalkenes bearing 2-pyridine group[3] despite the fact that 1,1-diarylalkane scaffolds, especially the 2-pyridine substituted chiral 1,1-diarylalkanes, are important intermediates in the synthesis of pharmaceuticals and natural products,[4] such as 2-(1-phenylethyl)pyridine and *R*-dimethindene analogues (Figure 1). Furthermore, only poor to moderate enantioselectivities have been obtained for asymmetric hydrogenation of 2-pyridyl alkenes.[3,5] The main reason can be attributed to the coordination effect of pyridine, which degrades the catalyst's activity and stereocontrol ability to some extent. In addition, the small difference between aryl groups and pyridine groups also makes it difficult to achieve high enantioselectivities. To solve this problem, the 2-pyridine substituted alkenes were always hydrogenated as *N*-oxide species.[5] Direct asymmetric hydrogenation of alkenes containing 2-pyridine group is still a challenge.

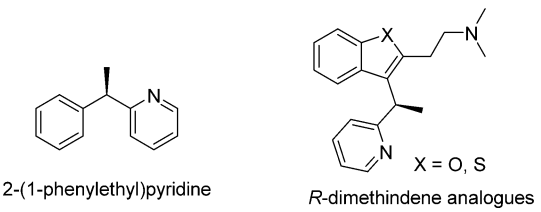


Figure 1. Pharmaceutical and biological active compounds containing 2-pyridyl ethane unit.

Recently we found that the 2-pyridine group could act as a directing group to achieve rhodium-catalyzed asymmetric hydrogenation of 2-pyridine ketones, affording 2-pyridine alcohols with high yields and excellent ee's.[6] We envision that the directing effect of the pyridine group can also play an important role in the asymmetric hydrogenation of 2-pyridine substituted alkenes under the right conditions, which is beneficial for the reaction to work smoothly and generate the desired products with high enantioselectivities. Herein, we disclose pyridine-directed rhodium-catalyzed asymmetric hydrogenation of 1,1-diarylalkenes.

In our initial studies, we chose the 2-(1-(*p*-tolyl)-vinyl)-pyridine (**1a**) as the standard substrate and the asymmetric hydrogenation was carried with $Rh(COD)_2BF_4$ under 10 bar of H_2 in CH_2Cl_2. First, (*R*)-Binapine, the best ligand for the asymmetric hydrogenation of 2-pyridine ketones, was examined. To our disappointment, it gave the desired product with very poor enantioselectivities, albeit with excellent activity (Table 1, entry 1). Then, other chiral diphosphorus ligands (Figure 2) were evaluated. Fortunately, we found that the DuanPhos, an electron-donating rigid bisphosphine ligand developed in our group, achieved 87% ee with full conversion (Table 1, entry 4). And other ligands, except TangPhos (62% ee, Table 1, entry 3) and Quinoxp* (65% ee, Table 1, entry 6), all gave less than 50% ee. Subsequently, the effect of metal precursors was evaluated. To our surprise, the iridium, which was frequently used in the asymmetric hydrogenation of alkenes, gave the desired product with excellent yield but no enantioselectivity (Table 2, entry 1). The anions of the

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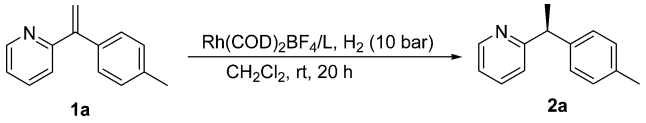
Table 1. Ligands Screening for the Asymmetric Hydrogenation of 1a[a]



entry	ligand	conversion[b] (%)	ee[c] (%)
1	(*R*)-Binapine	>99	24
2	(*R*)-Josiphos	>99	19
3	(1*S*,1*S*′,2*R*,2*R*′)-TangPhos	>99	62
4	(*Sc, Rp*)-DuanPhos	>99	87
5	(*S*)-Segphos	8	28
6	Quinoxp*	>99	65
7	Me-Duphos	37	45
8	*f*-BinaPhane	>99	37
9	C_3-TunePhos	32	2
10	DTBM-Biphep	48	40

[a]Unless otherwise noted, all reactions were carried out with a [Rh(COD)$_2$BF$_4$]/ligand/substrate (0.1 mmol) ratio of 1:1.1:100 in 1 mL of CH_2Cl_2 at room temperature under hydrogen (10 bar) for 20 h. [b]Determined by ^{1}H NMR. [c]Determined by HPLC analysis using a chiral stationary phase.

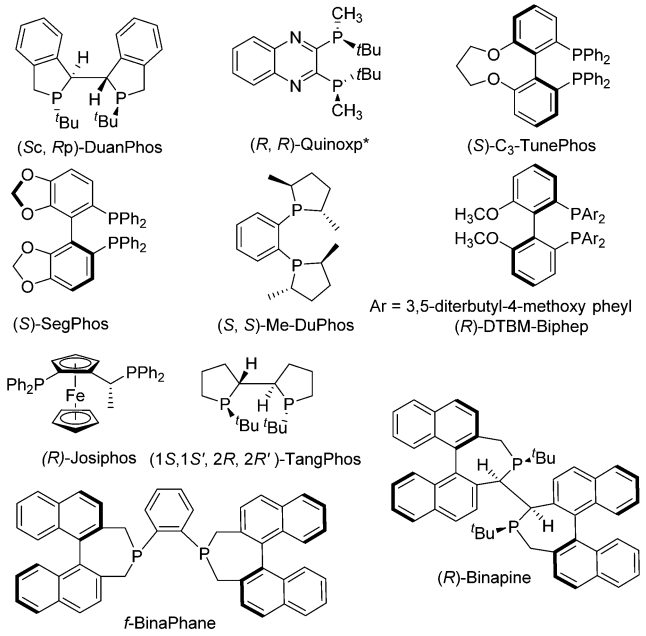
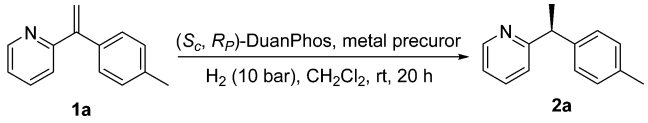


Figure 2. Ligands screened in the asymmetric hydrogenation of **1a**.

rhodium salts also greatly effected the enantioselectivities. When [Rh(COD)Cl]$_2$ was used, the ee of the product decreased significantly from 87% to 25% (Table 2, entry 2). We have also investigated the solvent effects and found the methanol was the most suitable solvent for this reaction. Other solvents had little effect on the enantioselectivities (Table 2, entries 3−10). When the reaction was conducted in methanol by using the (*Sc, Rp*)-DuanPhos/Rh(NBD)$_2$BF$_4$ complex as catalyst, the best results were obtained (Table 2, entry 11).

With the optimized conditions in hand, the substrate scope of asymmetric hydrogenation of 1,1-disubstituted 2-pyridine alkenes was investigated. As shown in Scheme 1, a series of 2-(1-arylvinyl)pyridines were hydrogenated very well and gave 2-(1-arylethyl)pyridines with good to excellent enantioselectivities (86−98% ee, **2a**−**2m**).[7] These results disclosed that the

Table 2. Condition Optimization of Asymmetric Hydrogenation of 1a[a]



entry	metal precursor	solvent	conversion[b] (%)	ee[c] (%)
1	[Ir(COD)Cl]$_2$	CH_2Cl_2	>99	0
2	[Rh(COD)Cl]$_2$	CH_2Cl_2	>99	25
3	Rh(COD)$_2$BF$_4$	EA	>99	87
4	Rh(COD)$_2$BF$_4$	EtOH	>99	89
5	Rh(COD)$_2$BF$_4$	MeOH	>99	90
6	Rh(COD)$_2$BF$_4$	$ClCH_2CH_2Cl$	>99	88
7	Rh(COD)$_2$BF$_4$	$CHCl_3$	>99	78
8	Rh(COD)$_2$BF$_4$	*i*PrOH	>99	86
9	Rh(COD)$_2$BF$_4$	CF_3CH_2OH	>99	89
10	Rh(COD)$_2$BF$_4$	THF	>99	84
11	Rh(NBD)$_2$BF$_4$	MeOH	>99	91

[a]Unless otherwise noted, all reactions were carried out with a metal precursor/ligand/substrate (0.1 mmol) ration of 1:1.1:100 in 1 mL of solvent at room temperature under hydrogen (10 bar) for 20 h. [b]Determined by ^{1}H NMR. [c]Determined by HPLC analysis using a chiral stationary phase.

electronic property and the position of substituent group on the benzene ring have an effect on the enantioselectivity. Generally, electron-withdrawing substituents have a positive effect on enantioselectivity for this reaction and gave a slightly higher ee than that with electron-donating groups (**2f**−**g**, **2l** vs **2a**, **2c**, **2k**). When a substituent was introduced to the *ortho* position of the phenyl group, it delivered the desired product with slightly lower enantioselectivities (**2d**, **2j**). It was worth noting that the directing effect could distinguish the 2-pyridine and 3-piridine groups precisely, giving excellent enantioselectivity (98% ee, Scheme 1, **2m**). Asymmetric hydrogenation of trisubstituted 2-pyridine alkenes was also conducted. Although the reactions proceeded smoothly, the enantioselectivities of the products decreased significantly. (*Z*)-2-(1-(*p*-Tolyl)prop-1-en-1-yl)-pyridine (**2n**) gave a 60% ee, and the (*E*)-2-(1-(*p*-tolyl)prop-1-en-1-yl)pyridine (**2o**) only gave a 73% ee with opposite optical rotation.

To determine if the directing effect of the pyridine group actually played a critical role in the asymmetric hydrogenation of 2-pyridine ethenes, substrates **1p**−**1r** were synthesized and hydrogenated (Scheme 1). When 3-pyridine ethene **1p** was tested under the same conditions, the asymmetric hydrogenation reaction did not work. When the 2-pyridine group was replaced with a phenyl group (**1q**) or other heterocyclic groups, such as thiophene (**1r**), these alkenes also showed no reactivity. All these results indicated that the 2-pyridine group actually functioned as a directing group in the asymmetric hydrogenation to improve the reactivity and enantioselectivity.

In summary, with the directing function of the pyridine groups, highly enantioselective rhodium-catalyzed asymmetric hydrogenation of 2-pyridine 1,1-diarylethenes was achieved, giving 2-pyridine substituted 1,1-diarylalkanes with excellent yields and enantioselectivities (up to 99% yield, up to 98% ee). This protocol provided an efficient method to prepare chiral 2-(1-arylethyl)pyridines and their derivatives. Further investigations on asymmetric hydrogenation by using the directing strategy are underway.

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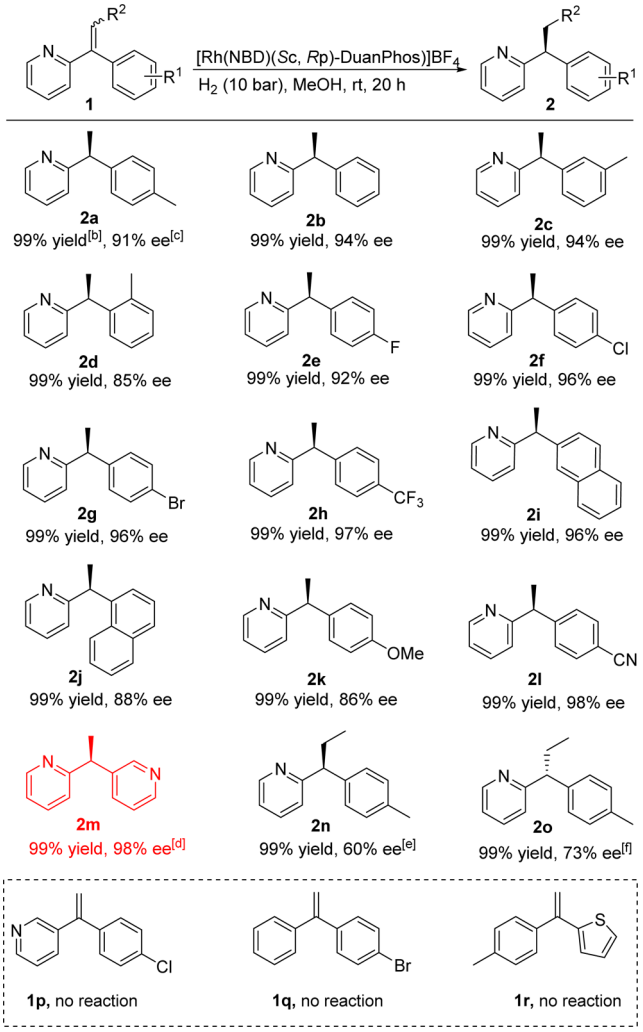
Scheme 1. Rhodium Catalyzed Asymmetric Hydrogenation of 1,1-Diarylalkenes[a]



[a]Unless otherwise noted, all reactions were carried out with a $[Rh(NBD)_2BF_4]$/(*Sc*, *Rp*)-DuanPhos/substrate (0.1 mmol) ratio of 1:1.1:100 in 1 mL of MeOH at room temperature under hydrogen (10 bar) for 20 h. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. [d]5 mol % Rh(NBD)(*Sc*, *Rp*-DuanPhos)BF_4 was used. [e](*Z*)-Alkene was used as substrate. [f](*E*)-Alkene was used as substrate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02262.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(7) The absolute configuration of compound **2b** was confirmed to be *S* by comparison specific rotation data within ref 5. All the other configurations are uncertain and based on the assumption that the configuration follows that of **2b**.

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