

Highly Efficient Rh(I)-Catalyzed Asymmetric Hydrogenation of Enamines Using Monodentate Spiro Phosphonite Ligands

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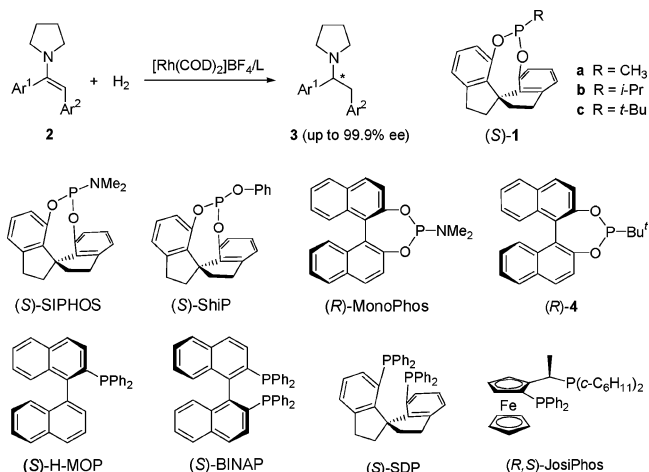
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Chiral amines are an important class of compounds in organic and pharmaceutical synthesis, and a great effort has been made to develop efficient synthetic methods for chiral amines. In the past decades, the catalytic asymmetric hydrogenation of functionalized enamines, such as α - and β -*N*-acylamino acrylates, and enamides have been extensively studied, and a great number of highly enantioselective protocols for the synthesis of enantiomer-enriched primary and secondary amines have been documented.¹ However, only a limited progress has been achieved in the direct preparation of chiral tertiary amines, which broadly occurred in the biologically active molecules and natural products,² by asymmetric hydrogenation of the corresponding *N,N*-dialkyl enamines. This is not surprising because one substantial drawback in the current approaches to asymmetric hydrogenation of enamides is the requirement of an *N*-acyl group in the substrate.³ This *N*-acyl group is considered indispensable for the substrate to form a chelate complex with metal of catalyst in transition state, giving a good reactivity and enantioselectivity. Up to now, only two groups have tackled the challenging class of *N,N*-dialkyl enamine substrates in the asymmetric hydrogenation.⁴ In 1994, Buchwald et al.⁵ reported the first example of catalytic asymmetric hydrogenation of simple enamines. By using 5 mol % chiral titanocene catalyst [(*S,S,S*)-(EBTHI)TiO₂-binaphtho] they achieved excellent enantioselectivities (up to 98% ee) in the hydrogenation of 1-(dialkylamino)-1-arylethenes. Few years later, Börner and co-workers⁶ used chiral Rh(I)-diphosphine complexes for this hydrogenation and obtained the chiral tertiary amines in moderate enantiomeric excesses (up to 72%). These results are very encouraging and suggested that new efficient catalysts are necessary for the development of highly enantioselective hydrogenation of simple nonfunctionalized enamines to give chiral tertiary amines in broad scope.

Recently, we demonstrated that the chiral monodentate phosphoramidites and phosphonites containing a 1,1'-spirobiindane scaffold were highly enantioselective ligands for the Rh-catalyzed asymmetric hydrogenation of *N*-(α -arylethenyl)-acetamides and *N*-acyl α - and β -dehydroamino acid derivatives.⁷ As a part of our sustained efforts in this area, we herein wish to report the asymmetric hydrogenation of *N,N*-dialkyl enamines using chiral spiro phosphonite ligands **1**, providing chiral tertiary amines in excellent enantiomeric excesses (up to 99.9%).

The chiral tertiary 1,2-diarylethanamine is a very useful unit; it widely exists in natural products such as benzyloisoquinolines.⁸ The catalytic asymmetric hydrogenation of *N,N*-dialkyl enamines is one of the most straightforward accesses to the optically active tertiary 1,2-diarylethanamines. In our study, the hydrogenation of (*E*)-1-(1-pyrrolidinyl)-1,2-diphenylethene (**2a**) was initially performed under 100 atm of H₂ in THF with the rhodium catalyst generated in situ from 1 mol % [Rh(COD)₂]BF₄ and 2.2 mol % phosphorus ligands. A brief screening on the chiral phosphorus ligands available in our laboratory showed that the diphosphine ligands including BINAP, SDP, and JosiPhos were inefficient in the reaction (ee \leq

Scheme 1

Table 1. Rh(I)-Catalyzed Asymmetric Hydrogenation of Enamine 2a, Optimizing Reaction Conditions^a

entry	ligand	solvent	PH ₂ (atm)	time (h)	addition (mol %)	ee (%) ^b
1	(<i>S</i>)- 1a	THF	100	48	none	14
2	(<i>S</i>)- 1b	THF	100	48	none	4
3	(<i>S</i>)- 1c	THF	100	48	none	33
4	(<i>S</i>)- 1c	THF	100	48	I ₂ (5)	71
5	(<i>S</i>)- 1c	THF	100	48	I ₂ (2)	83
6	(<i>S</i>)- 1c	THF	100	48	I ₂ (1)	77
7	(<i>S</i>)- 1c	Et ₂ O	100	48	I ₂ (2)	66
8	(<i>S</i>)- 1c	dioxane	100	48	I ₂ (2)	72
9	(<i>S</i>)- 1c	CH ₂ Cl ₂	100	48	I ₂ (2)	78
10	(<i>S</i>)- 1c	toluene	100	48	I ₂ (2)	60
11	(<i>S</i>)- 1c	DME	100	48	I ₂ (2)	20
12	(<i>S</i>)- 1c	MeOH	100	48	I ₂ (2)	12
13	(<i>S</i>)- 1c	THF	100	12	I ₂ /HOAc (2/50)	78
14	(<i>S</i>)- 1c	THF	30	12	I ₂ /HOAc (2/30)	78
15	(<i>S</i>)- 1c	THF	10	12	I ₂ /HOAc (2/20)	87
16 ^c	(<i>S</i>)- 1c	THF	10	24	I ₂ /HOAc (2/20)	77
17	(<i>S</i>)- 1c	THF	5	22	I ₂ /HOAc (2/20)	80
18	(<i>S</i>)- 1a	THF	10	12	I ₂ /HOAc (2/20)	32
19	(<i>S</i>)- 1b	THF	10	12	I ₂ /HOAc (2/20)	62
20	(<i>R</i>)- 4	THF	10	12	I ₂ /HOAc (2/20)	56
21	(<i>S</i>)-ShiP	THF	10	12	I ₂ /HOAc (2/20)	33

^a Reaction conditions: 1 mol % [Rh(COD)₂]BF₄, 2.2 mol % ligand, [substrate] = 0.125 M, room temperature, 100% conversion. ^b Determined by chiral HPLC using a chiralcel OD-H column. ^c With 0.5 mol % catalyst, 87% conversion.

10%). Most of monophosphorus ligands illustrated in Scheme 1 also gave very low enantioselectivity (ee \leq 14%) except for spiro phosphonite ligand (*S*)-**1c**, which provided chiral tertiary amine **3a** in 33% ee (Table 1, entry 3).

It was reported that the additives might play a crucial role for the high reactivity and enantioselectivity in the hydrogenations of simple olefins,⁹ ketones,¹⁰ and imines.¹¹ To improve the enantio-

selectivity in the hydrogenation of enamine **2a** catalyzed by Rh/(S)-**1c** complex, we investigated the effect of additives. When *o*-phthalimide, HOAc, or H₂SO₄ were added, the catalyst was strongly deactivated and only very low conversions were obtained. However, a promising result was obtained when I₂ was added. In the presence of 5 mol % I₂, the enantioselectivity of reaction was dramatically increased to 71% ee (entry 4). Adjusting the amount of I₂, we found that 2 mol % I₂ was suitable for achieving a high enantioselectivity (83% ee) (entry 5). Different solvents were then compared in the presence of 2 mol % I₂. A full conversion was obtained in all tested solvents. In addition to THF, the solvents including Et₂O, dioxane, CH₂Cl₂, and toluene also could be employed, albeit the enantioselectivities were slightly lower (60–78% ee). However, the reactions in MeOH and chelate solvent DME (1,2-dimethoxyethane) had very low enantioselectivities (entries 11 and 12). Although the addition of I₂ significantly improved the enantioselectivity of hydrogenation of enamine **2a**, the reaction rate was still too low.

Acid was often utilized to accelerate the reaction rate in the Ir(I)-catalyzed asymmetric hydrogenation of imines by preventing deactivation of the catalyst caused by the amine products.¹² It was mentioned above that the use of acetic acid alone in this Rh(I)-catalyzed hydrogenation of enamines strongly lowered the conversion. Surprisingly, when the acetic acid was used together with 2 mol % of I₂ in the hydrogenation of enamine **2a**, the reaction rate was remarkably increased. In the presence of 20–50 mol % of acetic acid the reaction time was shortened from 48 to 12 h without losing enantioselectivity. A more significant improvement brought about by the addition of I₂ and acetic acid was that the hydrogenation could proceed under a much lower pressure of H₂, which was beneficial to high enantioselectivity. For example, employing 2 mol % I₂ and 20 mol % acetic acid as additives, the hydrogenation of **2a** was completed in 12 h under 10 atm of hydrogen, affording the amine **3a** in 87% ee (entry 15). The comparison of ligands **1** under the optimized conditions showed that the enantioselectivity of catalyst was constantly enhanced as the size of R group in the ligands **1** became larger. The ligand **1c**, which contained a *tert*-butyl gave the best result. Other ligands listed in Scheme 1 were also evaluated in combination with iodine/acetic acid. Most of them showed no enantioselectivity, with ligands **4** (56% ee) and ShiP (33% ee) being exceptions.

A variety of (*E*)-1-(1-pyrrolidinyl)-1,2-diarylethenes **2** can be successfully hydrogenated using [Rh(COD)₂]BF₄/(S)-**1c** catalyst to produce the corresponding tertiary amines **3** in good to excellent ee values (Table 2). The electronic nature of the aryl groups of enamines **2** had a strong influence on the enantioselectivity of the reaction. The substrates with a Ar¹ connecting electron-donating groups such as Me or MeO have higher enantioselectivity (entries 2–6). However, on the Ar² side, a reverse effect was observed. The substrates with a Ar² connecting electron-withdrawing groups such as Cl, Br, and F on para-position gave higher enantioselectivity. The highest enantioselectivity (99.9% ee) was achieved in the hydrogenation of enamine **2n**, which has a 4-F on Ar² (entry 14). The effect of *N*-alkyl groups of enamine substrates on the enantioselectivity of reaction was also examined. When the pyrrolidine moiety was changed to piperidine and morpholine the ee values of hydrogenation products were lowered to 75% and 77%, respectively.

In summary, a highly enantioselective hydrogenation of simple *N*-unprotected enamines catalyzed by a Rh(I) complex of chiral spiro phosphonite ligand (S)-**1c** has been developed, which provided a straightforward method for the synthesis of chiral tertiary amines with excellent ee values. Further investigation will focus on the

Table 2. The Asymmetric Hydrogenation of Enamines **2** Catalyzed by Rh(I)/(S)-**1c** Complex^a

entry	Ar ¹	Ar ²	product	ee (%) ^b
1	C ₆ H ₅ (2a)	C ₆ H ₅	3a	87
2	4-MeC ₆ H ₄ (2b)	C ₆ H ₅	3b	91
3	3-MeC ₆ H ₄ (2c)	C ₆ H ₅	3c	90
4	2-MeC ₆ H ₄ (2d)	C ₆ H ₅	3d	90
5	4-MeOC ₆ H ₄ (2e)	C ₆ H ₅	3e	95
6	3,4-(MeO) ₂ C ₆ H ₃ (2f)	C ₆ H ₅	3f	99
7	4-ClC ₆ H ₄ (2g)	C ₆ H ₅	3g	73
8	C ₆ H ₅ (2h)	2-MeC ₆ H ₄	3h	94
9	C ₆ H ₅ (2i)	2-ClC ₆ H ₄	3i	93
10	C ₆ H ₅ (2j)	3-ClC ₆ H ₄	3j	90
11	C ₆ H ₅ (2k)	4-MeC ₆ H ₄	3k	80
12	C ₆ H ₅ (2l)	4-ClC ₆ H ₄	3l	96
13	C ₆ H ₅ (2m)	4-BrC ₆ H ₄	3m	97(R) ^c
14	C ₆ H ₅ (2n)	4-FC ₆ H ₄	3n	99.9
15	3-MeC ₆ H ₄ (2o)	4-FC ₆ H ₄	3o	90
16	4-MeOC ₆ H ₄ (2p)	4-FC ₆ H ₄	3p	95
17	4-MeOC ₆ H ₄ (2q)	4-ClC ₆ H ₄	3q	93

^a [Rh(COD)₂]BF₄/(S)-**1c**/I₂/HOAc/substrate = 1:2.2:2:20:100, [substrate] = 0.125 M, THF, rt, 10 atm H₂, 12 h, 100% conversion. ^b Determined by HPLC using chiral columns (see Supporting Information). ^c Determined by X-ray diffraction analysis (see Supporting Information).

reaction mechanism and the extension of this novel catalytic system to a broader range of enamines.

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Supporting Information Available: Experimental procedures, the characterizations of substrates and products, the analysis of ee values of hydrogenation products (PDF), and the crystal data and structure refinement for (R)-**3m**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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