

Rhodium-Catalyzed Enantioselective Hydrogenation of Oxime Acetates

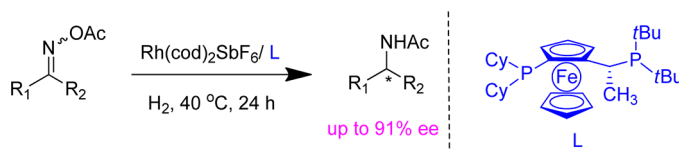
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ABSTRACT



Rh-catalyzed enantioselective hydrogenation of oxime acetates was first reported, which afforded a new approach for chiral amine synthesis.

Chiral amines and their derivatives are important synthetic targets and powerful pharmacophores for defining new pharmaceutical drugs.¹ In the past decade, many researchers have focused their efforts on the enantioselective synthesis of amines, and tremendous progress has been made toward truly practical methods.² New concepts and optimized methods are still needed to achieve both complete enantiocontrol and efficiency under different circumstances. The asymmetric reduction of oximes and their derivatives has been considered to be a facile and direct approach to chiral amine because of the ease of preparation and stability of oxime substrates.³ However, this area has been less explored over the last 10 years, and limited results have been achieved. Successful examples include borane-mediated reduction of oxime ethers.⁴ Itsuno and co-workers reported the first catalytic borane reduction of *O*-benzyl oxime in 1987.⁵ Recent research results from Fontaine, Zaidlewicz, and Ortiz-Marciales's groups showed

that chiral diphenylvalinolborane, oxazaborolidine, and spiroborate esters could serve as remarkable catalysts to afford chiral amines with high enantioselectivities.⁶ (Scheme 1, eq 1).

Asymmetric hydrosilylation of ketoximes is another reliable approach for this transformation. Brunner and co-workers developed the rhodium-catalyzed asymmetric hydrosilylation of ketoximes using DIOP as ligand (up to 36% ee)⁷ (Scheme 1, eq 2). Recently, Hidai reported asymmetric reduction of cyclic oximes by using Ph₂SiH₂ and a Ru-oxazolonylferrocenylphosphine catalyst.⁸ Lipase/palladium-catalyzed asymmetric transformations of ketoximes to chiral amines were also reported by Park and Kim.⁹

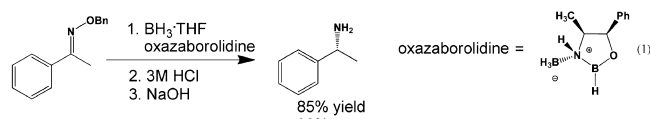
Ever since the success of the L-DOPA process, enantioselective hydrogenation has proven to be an efficient way

[†] Rutgers, The State University of New Jersey.[‡] Northwest Agriculture & Forestry University.(1) Nugent, T. C. *Chiral Amine Synthesis. Methods, Developments and Applications*; Wiley-VCH: New York, 2010.(2) Breuer, M.; Ditrach, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.(3) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753–819.(4) (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–84. (b) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2004**, *73*, 581–608. (c) Payette, J. N.; Yamamoto, H. *Boronic Acids (2nd Ed.)* **2011**, *2*, 551–590.(5) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395–398.(6) Selected examples: (a) Fontaine, E.; Namane, C.; Meneyrol, J.; Geslin, M.; Serva, L.; Roussey, E.; Tissandie, S.; Maftouh, M.; Roger, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2185–2189. (b) Krzeminski, M. P.; Zaidlewicz, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1463–1466. (c) Chu, Y.; Shan, Z.; Liu, D.; Sun, N. *J. Org. Chem.* **2006**, *71*, 3998–4001. (d) Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F. G.; Ayala, A. M.; Correa, W.; De Melvin, J. *Org. Lett.* **2007**, *9*, 1793–1795.(7) (a) Brunner, H.; Becker, R. *Angew. Chem., Int. Ed.* **1984**, *23*, 222–223. (b) Brunner, H.; Becker, R.; Gauder, S. *Organometallics* **1986**, *5*, 739–746.(8) Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* **2001**, 2360–2361.(9) (a) Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2008**, *73*, 4302–4304. (b) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099–4101.

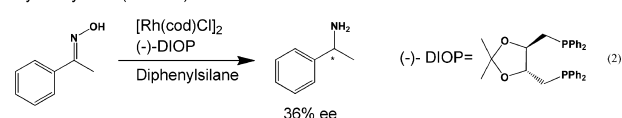
for the synthesis of chiral amines and their derivatives.¹⁰ Many practical catalytic systems have been developed for the enantioselective hydrogenation of enamines and imines.¹¹ However, until now, direct hydrogenation of simple ketoneoximes and their derivatives still remains a long-standing problem.¹² A typical example was reported by Chan in 1995 for the catalytic asymmetric hydrogenation of 1-acetonaphthone oxime with Rh chiral phosphine catalysts (Scheme 1, eq 3). It should be noted that the reaction can only proceed under high temperature (100 °C) and with long reaction time (5 days).^{12c}

Scheme 1. Previous Strategy for Asymmetric Reduction of Oximes and Oxime Derivatives

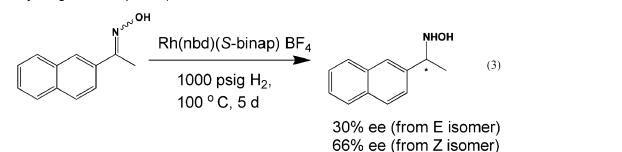
Borane reduction (Zaidlewicz)



Hydrosilylation (Brunner)



Hydrogenation (Chan)



Inspired by the success of *N*-acetylenamides and enol acetates as substrates for asymmetric hydrogenation,^{10a} we envisioned that ketoneoxime acetates might be significant substrates for hydrogenation.¹³ Recently, oxime esters have already gained much attention especially for their applications in the coupling reactions.¹⁴ Herein, we report the first enantioselective hydrogenation of ketoneoxime acetates.

We began our study by investigating the hydrogenation of **1a** as the model substrate. After initial screening of

Table 1. Selected Results from Initial Screening of Chiral Ligands for Rhodium-Catalyzed Hydrogenation of **1a**^a

entry	ligand	conv ^b (%)	ee ^c (%)
1 ^e	(<i>S</i>)-MonoPhos	<10	63
2	(<i>S</i>)-BINAP	10	14
3	(<i>R</i>)-MeO-BIPHEP	<5	nd
4	(<i>S</i>)-Segphos	15	3
5	(<i>S</i>)-C ₃ -TunePhos	17	5
6	(<i>S,S</i>)-CHIRAPHOS	10	35
7	(<i>S,S</i>)-BDPP	12	7
8	(<i>S</i>)-PhanePhos	14	19
9	(<i>S,S</i>)-Me-DuPhos	55	12
10	(<i>S,S</i>)-Et-DuPhos	52	27
11 ^d	(<i>S,S</i>)-Me-BPE	55	37
12	(<i>S,S</i>)-Ph-BPE	18	64
13 ^d	TangPhos	88	23
14 ^d	(1 <i>S</i> ,1' <i>S</i> ,1 <i>R</i> ,1' <i>R</i> ')-DuanPhos	82	15
15 ^d	(<i>S</i>)-ZhangPhos	85	12
16 ^d	(<i>S</i>)-BINAPINE	74	9
17 ^d	(<i>R</i>)-TCFP	>95	2
18	(<i>R</i>)-(<i>S</i>)-Mandyphos	<5	2
19	(<i>R</i>)-(<i>R</i>)-Walphos	<5	9
20	(<i>R</i>)-(<i>R</i>)-Ph-Taniaphos T1	13	14
21	(<i>R</i>)-(<i>R</i>)-Cy-Taniaphos T2	90	1
22	Josiphos L1	82	65
23	Josiphos L2	78	61
24	Josiphos L3	40	17
25	Josiphos L4	35	47
26	Josiphos L5	20	3
27	Josiphos L6	<5	nd

^a Unless otherwise mentioned, reaction conditions: Rh(cod)₂BF₄/ligand/substrate = 1:1.1:10, at 40 °C, under 50 atm of hydrogen for 24 h.

^b Conversions were determined by ¹H NMR of the crude product.

^c Determined by GC on a chiral phase. ^d [Rh(cod)L]BF₄ complex was used directly. ^e Rh(cod)₂BF₄/ligand = 1:2.1.

different combinations of metal complexes and ligands, we were surprised to find that using Rh(I)/phosphine complexes as catalyst afforded the corresponding chiral acetamide as the major product, rather than *O*-acetyl-*N*-(1-phenylethyl)hydroxylamine¹⁵ (Table 1). The MonoPhos ligand family was first tested, and (*S*)-MonoPhos was found to afford the highest ee (63%) (Figure 1). However, low catalytic activity was observed under our screening conditions (conversions < 10%). Atropisomeric bisphosphine ligands such as BINAP, SEGPHOS, MeO-BIPHEP, and TunePhos were tested with up to 14% ee albeit with low conversions. Low catalytic activity was also observed with ligands such as BDPP, CHIRAPHOS, and PhanePhos. Chiral bisphosphane ligands such as Me-DuPhos and Et-BPE improved the reaction conversions

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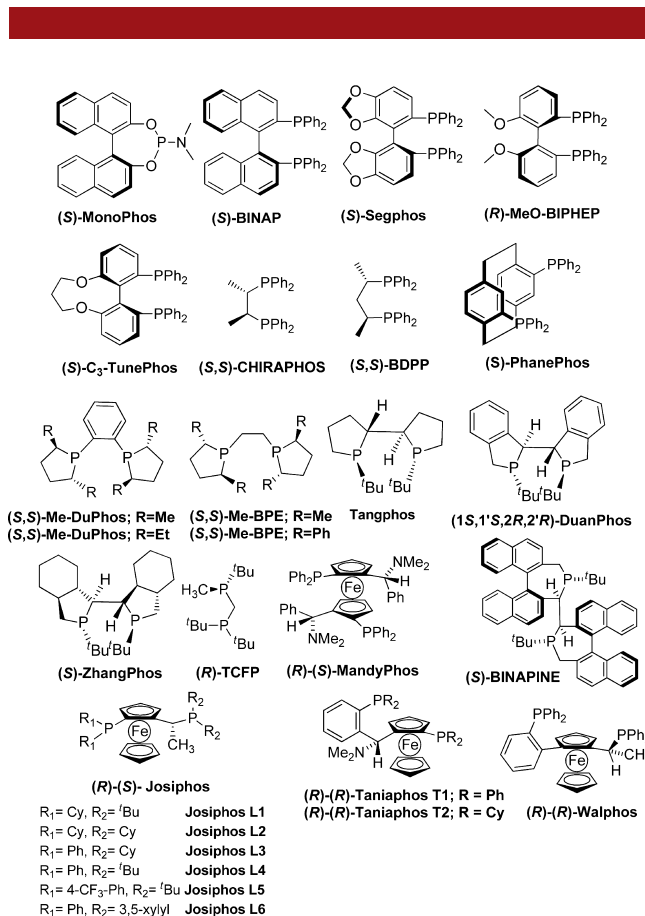
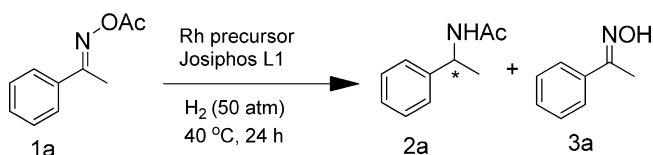


Figure 1. Selected phosphine ligands tested for the reaction.

(up to 55%) and enantioselectivities (37% ee). Based on the ligand effect observed, we hypothesized that electron-rich phosphine ligands are more favored for this reaction. We then performed screening of some electron rich *P*-chiral ligands such as TangPhos, DuanPhos, ZhangPhos, and BINAPINE. Up to 88% conversions were achieved by TangPhos and DuanPhos; however, only about 20% ee was provided. A three-hindered quadrant ligand TCFP gave almost complete conversion with low enantioselectivity (2% ee). We then focused on the ferrocene-based ligands. Walphos and Mandyphos showed little activity for the reaction. Cy-Taniaphos ligand afforded good conversion; however, almost racemic products were observed. To our delight, when Josiphos L1 was tested in the reaction, 65% ee was achieved in THF with 82% conversion (Table 1, entry 22).

Solvent screening revealed that the reaction was most efficient when conducted in THF or 1,4-dioxane (Table 2). Moreover, protic solvents such as MeOH and ⁱPrOH would completely lead to the corresponding oxime **3a** as final product. Further optimization showed that the enantioselectivity could be improved by using Rh(cod)₂SbF₆ as the Rh precursor in 1,4-dioxane (81% ee) (Table 2, entry 11). The yield could be improved by acylation of the product with Ac₂O due to some primary amine remained during the process (no ee value change observed after acylation).

Table 2. Optimization of the Reaction Conditions^a

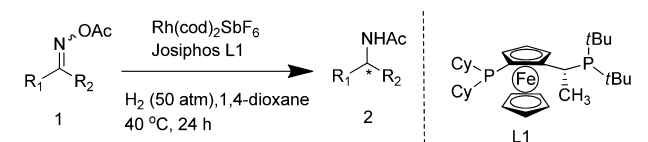


entry	Rh precursor	solvent	yield of 2a ^b (%)	ee ^c (%)
1	Rh(cod) ₂ BF ₄	CH ₂ Cl ₂	78	25
2	Rh(cod) ₂ BF ₄	THF	61	65
3	Rh(cod) ₂ BF ₄	toluene	57	45
4	Rh(cod) ₂ BF ₄	ethyl acetate	47	55
5	Rh(cod) ₂ BF ₄	1,4-dioxane	63	62
6	Rh(cod) ₂ BF ₄	MeOH	<5	n.d.
7	Rh(cod) ₂ BF ₄	ⁱ PrOH	<5	nd
8	Rh(nbd) ₂ BF ₄	THF	59	65
9	[Rh(cod)Cl] ₂ ^d	THF	48	68
10	Rh(cod) ₂ SbF ₆	THF	65	75
11	Rh(cod)₂SbF₆	1,4-dioxane	69	81

^a Unless otherwise mentioned, reaction conditions: Rh precursor/ligand/substrate = 1:1.1:10, at 40 °C, under 50 atm of hydrogen for 24 h.

^b Determined by ¹H NMR of the crude product after acylation with Ac₂O. ^c Determined by GC on a chiral phase. ^d [Rh(cod)Cl]₂/L1 = 1:2.2.

Table 3. Substrate Scope and Limitations^a



8	R ₁	R ₂	<i>E/Z</i> of 1	yield ^b (%)	ee ^{c,d} (%)
1	C ₆ H ₄	Me	<i>E</i> (1a)	69	81 (S)
2	4-MeC ₆ H ₄	Me	<i>E</i> (1b)	72	91 (S)
3	4-EtC ₆ H ₄	Me	<i>E</i> (1c)	76	91
4	4-FC ₆ H ₄	Me	<i>E</i> (1d)	80	90 (S)
5	4-ClC ₆ H ₄	Me	<i>E</i> (1e)	72	86 (S)
6	4-BrC ₆ H ₄	Me	<i>E</i> (1f)	76	85 (S)
7	4-CF ₃ C ₆ H ₄	Me	<i>E</i> (1g)	71	73 (S)
8	4-MeOC ₆ H ₄	Me	<i>E</i> (1h)	58	47 (S)
9	3-FC ₆ H ₄	Me	<i>E</i> (1i)	70	84
10	3-CF ₃ C ₆ H ₄	Me	<i>E</i> (1j)	65	82
11	3-ClC ₆ H ₄	Me	<i>E</i> (1k)	66	89
12	3-BrC ₆ H ₄	Me	<i>E</i> (1l)	74	83
13	3-MeC ₆ H ₄	Me	<i>E</i> (1m)	63	76
14	3-MeOC ₆ H ₄	Me	<i>E</i> (1n)	52	74
15	2-MeOC ₆ H ₄	Me	<i>E</i> (1o)	48	41
16	2-MeOC ₆ H ₄	Me	<i>E/Z</i> = 5:1	51	39
17	2-ClC ₆ H ₄	Me	<i>E/Z</i> = 3:1 (1p)	37	44
18	2-naphthyl	Me	<i>E</i> (1q)	68	60
19	C ₆ H ₅	Et	<i>E</i> (1r)	41	61
20	C ₆ H ₅	ⁿ Pr	<i>E</i> (1s)	45	53

^a Conditions: Rh(cod)₂SbF₆/ligand/substrate = 1:1.1:10, in 1,4-dioxane, at 40 °C, under 50 atm of hydrogen for 24 h. ^b Determined by ¹H NMR of the crude product after acylation with Ac₂O. ^c Determined by GC on a chiral phase. ^d Absolute configuration determined by comparison with literature (see the Supporting Information).

To further explore the efficiency and tolerance of the reaction, we subjected a series of substrates to asymmetric hydrogenation under the optimized conditions. Substrates bearing para-substituted methyl or ethyl groups gave 91% ee with moderate yields (Table 3, entries 2 and 3). Substrates with para-substituted electron-withdrawing groups on the aromatic ring were hydrogenated with good to high enantioselectivities (ee's up to 90%, entries 4–7). A methoxy group on the para-position caused a dramatic loss of enantioselectivity (entry 8). Substrates with meta-substituted moiety on the aromatic ring also gave comparable results with up to 89% ee (entries 9–13). However, ortho-substituted groups on the aromatic ring dramatically lower the reactivity and enantioselectivities of the substrates (entries 15–17). Moreover, *E/Z* conformers of ortho-substituted substrates were often obtained as a mixture and difficult to separate them from each other. Loss of enantioselectivities and activities were also observed when substrates with bulkier R₂ groups were tested (entries 19 and 20).

The reaction mechanism is still not clear. Similar enantioselectivities given by the *E/Z* substrate conformers may suggest the N–O bond cleavage before the hydrogenation process (Table 3, entries 15 and 16). Cleavage of the N–O bond in oxime carboxylates has been established

for Pd- and Cu-catalyzed systems,^{14a,b} but studies still remain rare for Rh(I)-involved reactions. Moreover, acylation of chiral primary amine with oxime acetates was observed and considered responsible for the final amide formation.

In conclusion, we have successfully applied Rh-catalyzed enantioselective hydrogenation of oxime acetates to give chiral acetamides, which afforded a new approach for the synthesis of chiral amines from oxime derivatives. Commercially available phosphorus-based ligands were screened, and the highest enantioselectivities were achieved by the Josiphos ligand family. Further studies focusing on mechanistic aspects and hydrogenation of other challenging substrates are ongoing.

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Supporting Information Available. Experimental details and NMR and GC spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.