Asymmetric Hydrogenation

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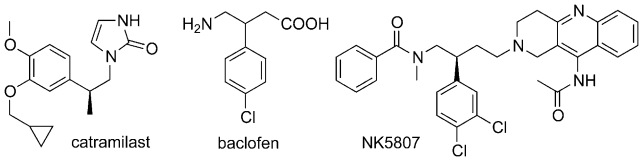
Highly Enantioselective Hydrogenation of β,β-Disubstituted Nitroalkenes**

Shengkun Li, Kexuan Huang, Bonan Cao, Jiwen Zhang, Wenjun Wu, and Xumu Zhang**

Enantiomerically pure nitroalkanes are valuable intermediates in organic synthesis. They can be easily converted to other versatile building blocks, such as amines, aldehydes, carboxylic acids, nitrile oxides, and denitrated compounds.[1] Structural motifs derived from chiral β-branched nitroalkanes can be found in many small molecule pharmaceuticals, such as catramilast, for the treatment of atopic dermatitis, the muscle relaxant baclofen,[2] and the asthma agent NK5807.



Many catalytic asymmetric methods are known to produce chiral β-branched nitroalkanes: 1) Several groups have reported the biocatalytic reduction of nitroalkenes using baker's yeast and reductases from *Lycopersicon esculentum*, *Saccharomyces carlsbergensis*, *Kluyveromyces lactis*, and *Yersinia bercovieri*.[3] 2) Carreira and Czekelius[4] have developed elegant chiral transfer hydrogenations of β,β-disubstituted nitroalkenes catalyzed by copper and iridium. The research group of Deng has demonstrated an efficient conjugate reduction of nitroalkenes using a chiral diamine–rhodium catalyst.[5] 3) Chiral thiourea-based organocatalysts have been applied in the asymmetric transfer hydrogenation of nitroalkenes.[6] 4) Versatile, highly enantioselective conjugate additions of carbon or phosphorus nucleophiles to nitroalkenes have also been reported by a number of groups.[7]

To the best of our knowledge, the direct hydrogenation of nitroalkenes with molecular H_2 has not yet been reported, despite the potential for high efficiency. Asymmetric hydrogenation of nitroalkenes has been a challenging problem and advances in this area will lead to an efficient, atom-economical approach to chiral β-branched nitroalkanes (Figure 1). Herein, we report the first highly enantioselective hydrogenation of β,β-disubstituted nitroalkenes to produce chiral β-branched nitroalkanes.

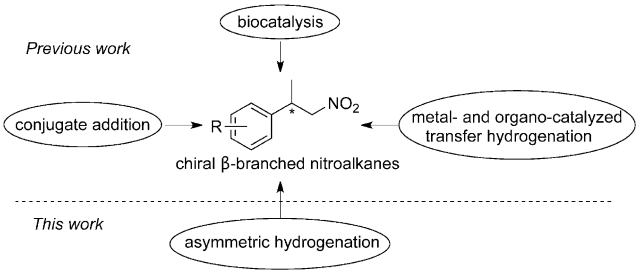


Figure 1. Different approaches to chiral β-branched nitroalkanes.

Apart from the importance of chiral nitroalkanes, the asymmetric hydrogenation of nitroalkenes is particularly attractive as these substrates are readily available and can be prepared by the Henry reaction or through the nitration of olefins (nitration of α-methylstyrene with N_2O_4,[4a,8] HNO_3,[3e] or CAN[3g,9]). In our preparation, β,β-disubstituted nitroalkenes **1a–v** were synthesized from substituted acetophenones through a Wittig reaction followed by CAN-catalyzed nitration (CAN = ceric ammonium nitrate; see the Supporting Information for details).

Our initial evaluation began with the asymmetric hydrogenation of model substrate **1a** with a series of catalysts. Poor results were obtained using Ru–bidentate phosphine catalysts, which gave low conversion and/or low *ee*. A number of Rh complexes of monodentate phosphine ligands were also evaluated, also with poor results (see the Supporting Information). Rh complexes with bidentate phosphines, such as Rh-Duanphos, Et-Duphos, Tangphos, or Me-Pennphos complexes (Figure 2) gave low enantioselectivities, albeit with good conversions (Table 1, entries 1–4). In some cases, the isomerization of **1a** was detected (Table 1, entries 1 and 4). Chiral biaryl bisphosphorus ligands (*S*)-Segphos and (*R*)-MeO-Biphep (Table 1, entries 5 and 6) showed no activity. (*S*)-C_3-Tunephos showed some activity and selectivity (31% *ee*, Table 1, entry 7). Other types of bidentate diphosphine ligands showed either significantly lower enantioselectivities with higher isomerization (Table 1, entry 8, f-Ketalphos) or no reactivity (Table 1, entry 9, (*R*)-QuinoxP).

We were gratified to find that the commercially available ferrocene ligand Josiphos-1 (Figure 2; Table 1, entry 10) gave a promising result with 87% conversion, 56% *ee*, and no

[*] S. Li, J. Zhang, Prof. W. Wu
Institute of Pesticide Science and College of Science
Northwest Agriculture & Forestry University
Yangling, Shaanxi 712100 (China)
E-mail: wuwenjun@nwsuaf.edu.cn
wenjun_wu@263.com
S. Li, K. Huang, B. Cao, Prof. X. Zhang
Department of Chemistry and Chemical Biology and
Department of Pharmaceutical Chemistry
Rutgers, the State University of New Jersey
Piscataway, NJ 08854 (USA)
E-mail: xumu@rci.rutgers.edu
Homepage: http://rutchem.rutgers.edu/~xumuweb/

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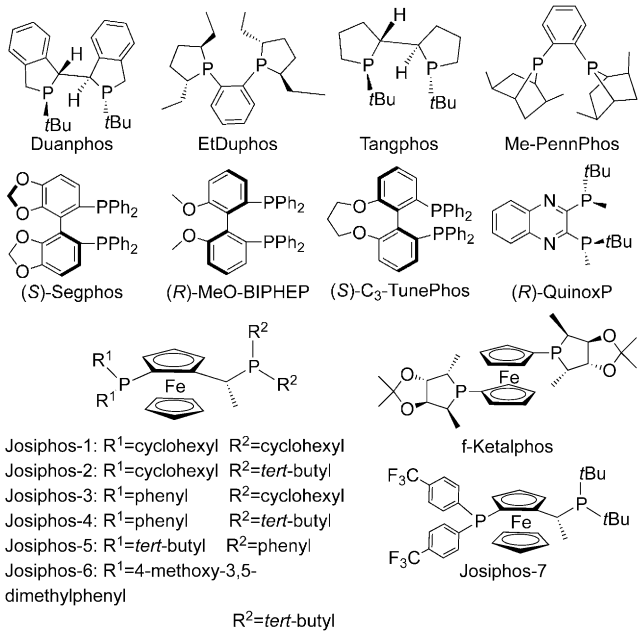
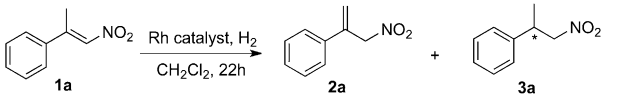


Figure 2. Structures of the ligands tested.

Table 1: Ligand screening for the Rh-catalyzed asymmetric hydrogenation of **1a**.[a]



Entry	Ligands	Distribution of products [%][b]			*ee* [%][c]
		1a	**2a**	**3a**	
1	Duanphos	2	20	78	21
2	Et-Duphos	0	0	100	10
3	Tangphos	26	0	74	7
4	Me-Pennphos	9	3	88	18
5	(*S*)-Segphos	100	0	0	NA
6	(*R*)-MeO-Biphep	100	0	0	NA
7	(*S*)-C_3-Tunephos	72	18	10	31
8	f-Ketalphos	47	18	35	7
9	(*R*)-QuinoxP	100	0	0	NA
10	Josiphos-1	13	0	87	56
11	Josiphos-2	7	0	93	65
12	Josiphos-3	0	0	100	65
13	Josiphos-4	0	0	100	80
14	Josiphos-5	80	0	20	15
15	Josiphos-6	75	8	17	3
16	Josiphos-7	0	0	100	85
17	Walphos	44	4	52	22
18	Taniaphos	77	7	16	55
19	Mandyphos	35	4	61	2
20	Josiphos-7[d]	0	0	100	79
21	Josiphos-7[e]	24	2	74	83
22	Josiphos-7[f]	0	0	100	81
23	Josiphos-7[g]	0	0	100	89

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(cod)_2]BF_4$/ligand/substrate ratio of 3:3:100, in CH_2Cl_2, at 45 °C, under hydrogen (60 atm) for 22 h. [b] The molar ratio was determined by ^1H NMR spectroscopy of the crude product. [c] Enantiomeric excess was determined by HPLC analysis on a chiral phase. [d] $[Rh(cod)Cl_2]$ as metal source. [e] $[Rh(acac)(CO)_2]$ as metal source. [f] $[Rh(acac)(C_2H_4)_2]$ as metal source. [g] $[Rh(NBD)_2]SbF_6$ as metal source. acac = acetyl acetonate, cod = 1,5-cyclooctadiene, NA = not available.

isomerization. A series of Josiphos ligands were then tested (Table 1, entries 11–16). Fine-tuning mainly focused on changes in the substituents on the two phosphines of Josiphos-1. When the phosphine connected with the chiral carbon was substituted with a bulkier and electron-rich *t*Bu group (Josiphos-2), the enantioselectivity was improved to 65% and high conversion was obtained (93%; Table 1, entry 11). When the cyclohexyl group on the other phosphine was changed to an electron-withdrawing phenyl group (Josiphos-3), complete conversion and 65% *ee* was obtained (Table 1, entry 12). These results motivated us to test Josiphos-4, which gave 80% *ee* with complete conversion (Table 1, entry 13). When the isomer (Josiphos-5) of Josiphos-4 was used, both the conversion and the enantioselectivity dropped dramatically (20% conversion, 15% *ee*; Table 1, entry 14). Switching to bulkier and electron-donating groups on the phenyl ring of Josiphos-4 (Josiphos-6) led to the worst result (Table 1, entry 15). Further evaluation of the substituent effects on the enantioselectivity and conversion led us to select Josiphos-7 as the ligand of choice for this hydrogenation; when tested, it gave 100% conversion and 85% *ee* (Table 1, entry 16). Other types of ferrocene diphosphine ligands, such as Walphos, Taniaphos, and Mandyphos, were also examined, but showed either significantly lower enantioselectivities or reactivities (see the Supporting Information).

With Josiphos-7, we screened other Rh sources with different counterions, and found that, except for $[Rh(acac)(CO)_2]$, the others were able to produce full conversion. The complex $[Rh(nbd)_2]SbF_6$ (nbd = 2,5-norbornadiene) gave the best enantioselectivity (89% *ee*, Table 1, entry 23). Reducing the reaction temperature to 35 °C and the H_2 pressure to 50 atm improved the enantioselectivity to 95% *ee*, without loss in conversion (Table 2, entry 1).

The choice of solvent plays a critical role in this Rh–Josiphos catalyst system. A slight decrease in conversion and selectivity was detected when using dichloroethane (DCE;

Table 2: Solvent screening for the Rh-catalyzed asymmetric hydrogenation of **1a**.[a]

Entry	Solvent	Catalyst loading [%]	Conv. [%][b]	*ee* [%][c]
1	CH_2Cl_2	3	>99	94
2	DCE	3	91	90
3	ethyl acetate	3	17	44
4	MeOH	3	42	17
5	toluene	3	14	NA
6	1,4-dioxane	3	20	14
7	THF	3	<2	NA
8	TFE	3	81	55
9	CH_2Cl_2	1	30	92
10	CH_2Cl_2	1.5	>99	94
11[d]	CH_2Cl_2	2	45	95
12[e]	CH_2Cl_2	1	>99	80

[a] Unless otherwise noted, the catalyst was produced in situ from a 1:1.1 mixture of Josiphos-7/$[Rh(nbd)_2]SbF_6$. All reactions were carried out at 35 °C, under hydrogen (50 atm) for 22 h. [b] Reaction conversions were determined by ^1H NMR spectroscopy. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] 22 °C. [e] 55 °C. DCE = dichloroethane, NA = not available, nbd = 2,5-norbornadiene, TFE = trifluoroethanol.

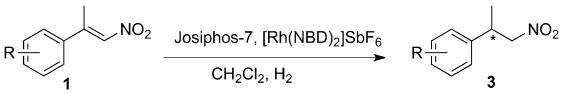
Table 2, entry 2). Poor conversions and enatioselectivities were observed when using ethyl acetate, MeOH, toluene, dioxane, and THF (Table 2, entries 3–7), and only moderate enantioselectivity was obtained in trifluoroethanol (TFE), although the conversion was good (Table 2, entry 8). Optimization of catalyst loading and temperature, resulted in 94.5% *ee* in the asymmetric hydrogenation of nitroalkene **1a** (Table 2, entry 10).

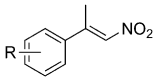
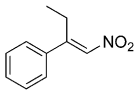
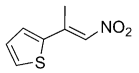
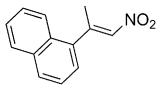
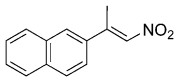
The hydrogenation appears to be sensitive to the position of the substituent on the aromatic ring, low conversion was observed when the substituent was in the *ortho* position, regardless of whether it was electron-donating or electron-withdrawing (Table 3, entries 2 and 3). This may be attributed to the steric hindrance produced by a group in the *ortho* position on the substrate. When the substituent was located in other ring positions, all substrates were hydrogenated with uniformly high conversions and enantioselectivities (Table 3, entries 4–18). Compared with the *ortho*-bromo substrate (Table 3, entry 2), nitroalkenes with a bromo substituent in the *meta* or *para* positions gave full conversions with good enantioselectivities (Table 3, entries 6 and 12). When a methyl substituent in the *ortho* position was replaced with one in the *para* position, results were significantly improved, giving both complete conversion and good enantioselectivity (Table 3, entries 3 and 16). Interestingly, a *para*-methoxy group resulted in 92% *ee* (Table 3, entry 15), whereas a *meta*-methoxy-substituted substrate gave up to 96% *ee* with full conversion (Table 3, entry 9). Enantioselectivities for the hydrogenation of halogen-substituted nitroalkenes are high, and followed the trend Br > Cl > F (Table 3, entries 4–6, 10–12). However, an iodo-substituted nitroalkene gave a slightly reduced stereoselectivity (93% *ee*; Table 3, entry 13).

The introduction of a trifluoromethyl group in the *meta* or the *para* positions of the phenyl ring reduced enantioselectivities to 86% and 92%, respectively (Table 3, entries 7 and 14). This may be a consequence of the larger Van der Waals volume of a CF_3 group; the further erosion in *ee* when a 3,5-ditrifluoromethyl substrate was used (82% *ee*; Table 3, entry 8) supports this theory. Substrates with *para*-methyl or *para*-ethyl groups gave slightly poorer results, 92% and 91% *ee*, respectively (Table 3, entries 16 and 17), whereas a sterically hindered *tert*-butyl group offered a good result (94% *ee*; Table 3, entry 18). A slight increase in enantioselectivity was observed when the methyl group in the β-position of nitroolefin **1a** was replaced by an ethyl group (96% *ee*; Table 3, entry 19). This method was also successfully applied to the asymmetric hydrogenation of heterocyclic substrate **1t**, which provided the product in up to 96% *ee* (Table 3, entry 20). Nitroalkenes substituted with 1- or 2-naphthyl groups afforded β-chiral nitroalkanes in 94% *ee* and 92% *ee*, respectively, and with good conversion (Table 3, entries 21 and 22).

In conclusion, we have developed a highly enantioselective hydrogenation of β-aryl-β-alkyl disubstituted nitroalkenes to provide enantiomerically pure nitroalkanes, which are versatile precursors in chemical synthesis. The resulting products provide an approach to valuable chiral amines, which are otherwise difficult to attain. The method described herein is the first report of the highly enantioselective hydrogenation of nitroalkenes. Further studies are in progress with the aim of exploring the mechanism of this asymmetric reaction and expanding substrate scope to ultimately develop more efficient and selective systems.

Table 3: Rh-catalyzed asymmetric hydrogenation of β,β-disubstituted nitroalkenes.[a]



Entry	Substrate	Product	Conv. [%][b]	*ee* [%][c]
				
1	R = H (**1a**)	**3a**	>99(92)	94
2	R = 2-Br (**1b**)	**3b**	50(90)	96
3[d]	R = 2-Me (**1c**)	**3c**	30(91)	92
4	R = 3-F (**1d**)	**3d**	>99(90)	93
5	R = 3-Cl (**1e**)	**3e**	85(88)	94
6	R = 3-Br (**1f**)	**3f**	>99(90)	95
7	R = 3-CF_3 (**1g**)	**3g**	>99(90)	86
8	R = 3,5-$(CF_3)_2$ (**1h**)	**3h**	>99(86)	82
9	R = 3-OMe (**1i**)	**3i**	>99(92)	96
10	R = 4-F (**1j**)	**3j**	>99(91)	89
11	R = 4-Cl (**1k**)	**3k**	>99(92)	93
12	R = 4-Br (**1l**)	**3l**	>99(92)	96
13	R = 4-I (**1m**)	**3m**	>99(88)	93
14	R = 4-CF_3 (**1n**)	**3n**	>99(90)	92
15	R = 4-OMe (**1o**)	**3o**	>99(94)	92
16	R = 4-Me (**1p**)	**3p**	>99(95)	92
17	R = 4-Et (**1q**)	**3q**	90(93)	91
18	R = 4-*t*Bu (**1r**)	**3r**	>99(94)	94
19	 (**1s**)	**3s**	>99(94)	96
20[d]	 (**1t**)	**3t**	60(84)	96
21	 (**1u**)	**3u**	85(90)	94
22	 (**1v**)	**3v**	95(90)	92

[a] The catalyst was produced in situ with CH_2Cl_2 as solvent. Unless otherwise noted, the reaction was run with a 1.5:1.7:100 mixture of Josiphos-7/$[Rh(nbd)_2]SbF_6$/substrates. All reactions were carried out at 35 °C, under hydrogen (50 atm) for 22 h. [b] The conversion was determined by HPLC and ^{1}H NMR analysis, data in parentheses is the yield of isolated product based on consumed starting material. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] 3% of the catalyst was consumed. nbd = 2,5-norbornadiene.

Experimental Section

General hydrogenation procedure: A stock solution was made by mixing $[Rh(nbd)_2]SbF_6$ with Josiphos-7 in a 1:1.1 molar ratio in CH_2Cl_2 at room temperature for 15 min in a nitrogen-filled glovebox.

An aliquot of the catalyst solution (0.2 mL, 0.0015 mmol) was transferred by syringe into a vial containing the substrate (0.1 mmol) in anhydrous CH_2Cl_2 (1.8 mL). The vials were subsequently transferred into an autoclave, which then underwent three cycles of flushing with hydrogen gas by pressurizing to 50 atm and then depressurizing. The reaction was then stirred under H_2 (50 atm) at 35 °C for 22 h. The autoclave was cooled to room temperature and the hydrogen gas was released slowly and carefully. The solution was then concentrated and passed through a short column of silica gel (eluant: CH_2Cl_2) to remove the metal complex. The *ee* values of all compounds were determined by HPLC analysis on a chiral stationary phase.

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