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Catalytic Enantioselective Hydrogenation of *N*-Alkoxycarbonyl Hydrazones: A Practical Synthesis of Chiral Hydrazines

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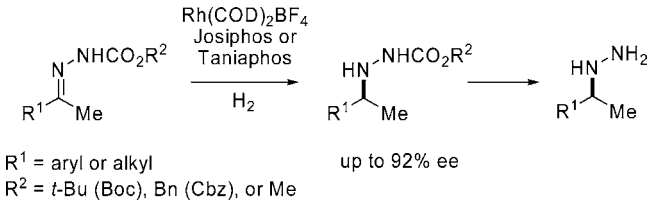
ABSTRACT



An enantioselective hydrogenation of hydrazones catalyzed by Rh complexes (Rh-Josiphos or Rh-Taniaphos) has been developed. The protocol can be applied to hydrazones with three different protective groups (Boc, Cbz, and methoxycarbonyl), allowing for selective deprotection and further elaboration of the hydrazine products in the presence of other functional groups.

The development of enantioselective hydrogenation of a C═N bond has received considerable attention as it provides a convenient access to a wide variety of compounds bearing C−N bonds with chiral stereogenic centers,[1] including precursors to numerous natural products and other biologically important compounds. One of the key factors in the development of enantioselective hydrogenation of imines is the choice of substituent on the nitrogen atom, which has proven to have critical influence on the reactivity and selectivity. *N*-Benzyl and *N*-aryl imines are commonly used as substrates for the enantioselective hydrogenations and offer opportunities for selective deprotection under different conditions. Cyclic imines have also been extensively studied as substrates. On the other hand, examples of the use of heteroatom-substituted imines[2] as substrate are rather limited except for sulfonyl and phosphinyl groups that are introduced as the protective groups.[3] In 1991, Burk et al. reported an asymmetric hydrogenation of *N*-acyl hydrazones catalyzed by Rh−Duphos complexes.[4] The resulting hydrazines can be transformed into chiral amines by reductive cleavage of the N−N bond. The hydrazine itself also constitutes an important class of building blocks to form various heterocyclic compounds.

In connection with our program to synthesize a pharmaceutical intermediate, we needed to prepare a large quantity of unprotected chiral hydrazine with an ester moiety on the phenyl ring (**1**, Figure 1).

(1) For recent reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Spindler, F.; Blaser, H.-U. *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 3, Chapter 34, pp 1193.

(2) Burk et al. reported the use of oximes as precursor to enamides, which could then be hydrogenated to give chiral amines. See: Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. For asymmetric reductive acylation of ketoximes, see: Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2008**, *73*, 4302.

(3) (a) Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2001**, *343*, 68. (b) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462. (c) Wang, Y.-Q.; Zhou, Y.-G. *Synlett* **2006**, 1189. (d) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832. (e) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766. (f) Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *J. Org. Chem.* **2007**, *72*, 3729. (g) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, *10*, 2071.

(4) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399.

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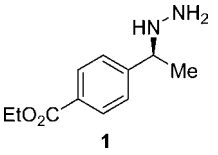

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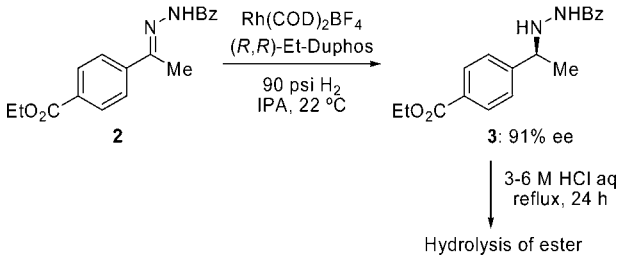
Figure 1. Unprotected hydrazine with an ester group as a synthetic target.

First of all, we repeated the Burk hydrogenation protocol to prepare **1** in an enantioselective manner. As reported in the literature, the hydrogenation of *N*-benzoyl-protected hydrazone **2** in the presence of Rh-Et-Duphos catalyst produced the corresponding hydrazine (**3**) with 91% ee (Scheme 1). In order to covert **1** to our pharmaceutical

Scheme 1. Hydrogenation of a *N*-Benzoyl-Protected Hydrazone Catalyzed by a Rh−Duphos Complex and Deprotection of the Benzoyl Group in the Presence of an Ester



2 3: 91% ee

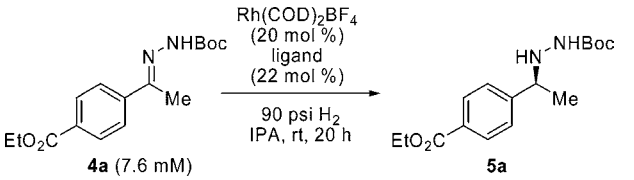
intermediate, we needed to deprotect the benzoyl group without affecting the ester moiety. When the deprotection was conducted under acidic conditions (aq HCl), however, the ester group was hydrolyzed in addition to the deprotection of benzoyl group to give the corresponding hydrazino acid, which was difficult to isolate from the aqueous reaction mixtures. It is also reported by Burk that this type of hydrazines can readily racemize under these deprotection conditions.[4]

It was highly desirable for us to prepare the unprotected hydrazine with the ester group retained. This would be made possible by the use of a more labile protective group such as a Boc group. When the Burk hydrogenation protocol was applied to a Boc-protected hydrazone **4a**, however, the corresponding product (**5a**) was obtained in a lower yield with only about 20% ee.

This result led us to develop a new catalyst system that would open direct access to an enantioselective synthesis of Boc-protected hydrazines. First, a wide variety of chiral ligands were screened using **4a** as the substrate in the presence of 20 mol % $Rh(COD)_2BF_4$ in IPA as solvent under dilute conditions (Table 1, Figure 2). As a result, some bidentate phosphine ligands were identified to provide the product with good to excellent enantioselectivities.

Some of those ligands that gave the best selectivities in the initial screening were examined further under different

Table 1. Selected Results from Initial Screening of Chiral Ligands for Rhodium-Catalyzed Hydrogenation of **4a** under Dilute Condition



4a (7.6 mM) **5a**

entry	ligand	convn[a] (%)	ee (%)
1	(*S*)-P-Phos (Ar = 3,5-$Me_2C_6H_3$)	28	91
2	(*R*)-(*S*)-Josiphos (Ar = Ph, R = *t*-Bu) (**6**)	22	91
3	(*S*)-Synphos	44	84
4	(+)-tetraMe-BITIOP	79	82
5	(*S*)-Ph-Solphos	62	81
6	(*S*)-P-Phos (Ar = Ph)	18	77
7	(*S*)-MeO-BIPHEP	39	76
8	(*R*)-(*S*)-Mandyphos	18	75
9	(*R*)-(*S*)-Josiphos (Ar = 4−F-C_6H_4, R = *t*-Bu)	5	74
10	(−)-Norphos	81	64
11	(*S*)-BINAP	21	45
12	(*R*)-(*S*)-Josiphos (Ar = Ph, R = *c*-hex)	3	31
13	(*S*)-(*R*)-Josiphos (Ar = *o*-tol, R = *t*-Bu)	5	26
14	(*R*,*R*)-*i*-Pr-Duphos	98	24
15	(*R*,*R*)-Et-Duphos	22	23
16	(*R*,*R*)-Diop	29	22
17	(*R*,*R*)-Chiraphos	7	18
18	(*S*)-Tol-BINAP	20	17

[a] Conversions were determined on the basis of area % by HPLC (230 nm). The hydrogenation reactions generally showed clean conversions.

conditions. As a result, a Josiphos ligand (**6**, Ar = Ph, R = *t*-Bu)[5] was found to be most suitable to our purpose in terms of selectivity, reactivity, and immediate availability in a large quantity at that time.

Thus, the reaction conditions were optimized using Rh-**6** as the catalyst. Table 2 summarizes solvent effects. Although good to excellent selectivities were obtained in all solvent systems except for CH_2Cl_2, the conversions were low in some solvents such as IPA, presumably due to low solubility of the hydrazone.

Further optimization revealed that the hydrogenation was most efficient when conducted in MeOH as solvent at a higher temperature (50 °C) under 300 psi H_2. When hydrazone **4a** was subjected to hydrogenation under these conditions in the presence of 0.75 mol % catalyst, the desired product (**5a**) was obtained in near quantitative yield with 86% ee (Table 3, entry 1).

The present protocol was applied to a variety of hydrazones to investigate the scope and limitations of the method (Table 3). The hydrazones (**4**) were readily prepared from the corresponding ketones and isolated by crystallization as single geometric isomers.[6] Boc-hydrazones prepared from different acetophenones (**4a**−**d**) generally gave good to

(5) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

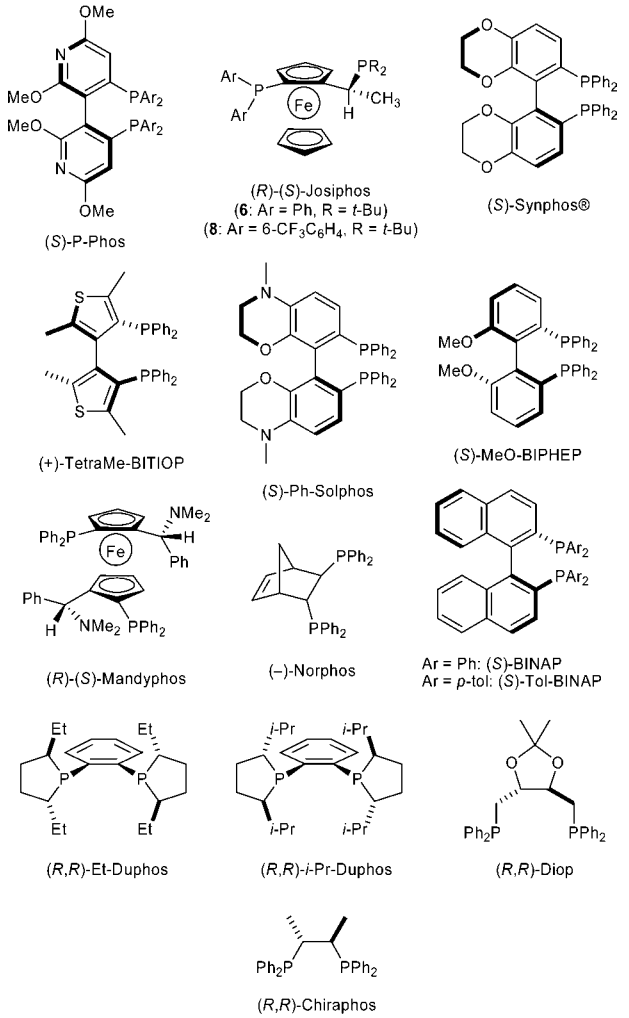
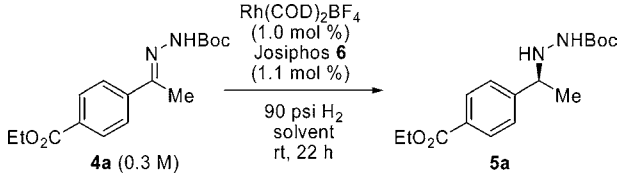


Figure 2. Some chiral ligands used for screening.

excellent results (84−91% ee) (entries 1−4). Hydrazone **4e**, derived from benzylacetone, was also applicable albeit with a lower selectivity (64% ee) (entry 5). Interestingly, hydrazone **4f**, prepared from methyl pyruvate, also gave an excellent conversion with moderate enantioselectivity (44% ee) under the same conditions without further optimization (entry 6).

In order to expand the scope of the method, hydrazones with different protective group (methoxycarbonyl and Cbz) were also examined (Table 4). Gratifyingly, both hydrazones produced the corresponding hydrazine with good enantioselectivities (73−78% ee) when Rh-**6** was used as the catalyst (entries 2 and 4). We then conducted further catalyst screening to find out the best system for these protective groups. As a result, the selectivities were

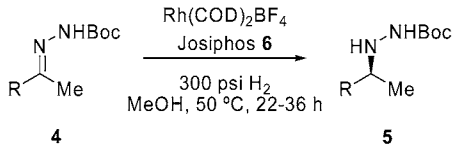
Table 2. Solvent Screening Using Rh-Josiphos Catalyst



entry	solvent	convn[a] (mol %)	ee (%)
1	MeOH	87	92
2	EtOH	63	91
3	IPA	30	86
4	THF	77	89
5	CH_2Cl_2	36	45
6	20% H_2O/IPA	83	84

[a] Conversions (mol %) were determined on the basis of HPLC assay.

Table 3. Substrate Scope and Limitations

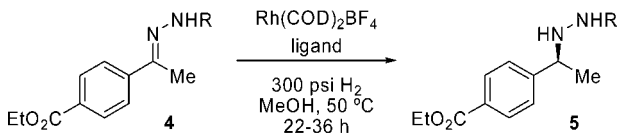


4a,**5a**: R = 4-EtOCO-C_6H_4- **4d**,**5d**: R = 4-MeO-C_6H_4-
4b,**5b**: R = 4-Br-C_6H_4- **4e**,**5e**: R = $PhCH_2CH_2$-
4c,**5c**: R = Ph- **4f**,**5f**: R =MeOCO-

entry	hydrazone	product	cat. (mol %)	convn[a] (%)	ee (%)
1	**4a**	**5a**	0.75	99[b]	86
2	**4b**	**5b**	1.5	100	91
3	**4c**	**5c**	1.5	99	86
4	**4d**	**5d**	1.5	100	84
5	**4e**	**5e**	1.5	100	64
6	**4f**	**5f**	1.5	97	44

[a] Conversions were determined on the basis of area % by HPLC (220 nm). The hydrogenations generally showed clean conversions. [b] The chemical yield was determined to be near quantitative by HPLC assay.

Table 4. Hydrogenation of Hydrazones with Different Protective Groups



4a,**5a**: R = CO_2t-Bu (Boc) **4h**,**5h**: R = CO_2Bn (Cbz)
4g,**5g**: R = CO_2Me

entry	4/5	ligand	cat. (mol %)	convn[a] (%)	ee (%)
1	**4a/5a**	**6**	0.75	99[b]	86
2	**4g/5g**	**6**	1.5	99	73
3[c]	**4g/5g**	**7**	5.0	97	88
4	**4h/5h**	**6**	1.5	100	78
5[d]	**4h/5h**	**8**	5.0	99	91

[a] Conversions were determined on the basis of area % by HPLC (220 nm). The hydrogenations generally showed clean conversions. [b] The chemical yield was determined to be near quantitative by HPLC assay. [c] Solvent: 1,2-dichloroethane. [d] Solvent: 1,2-dichlorobenzene.

significantly improved when Taniaphos (**7**)[7] (entry 3, Figure 3) was used as ligand for hydrazone **4g** and Josiphos **8** (entry 5, Figure 3) for **4h**.

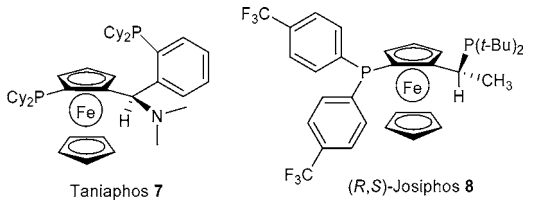


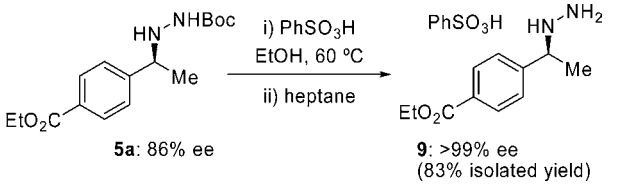
Figure 3. Chiral ligands that afforded best selectivities for hydrogenation of hydrazones **4g** and **4h**.

With an efficient hydrogenation method in hand, we turned our attention to the selective deprotection of the hydrazine product for further elaboration. Unlike the benzoyl-protected hydrazine (**3**), the Boc hydrazine (**5a**) was easily deprotected by treatment with benzenesulfonic acid in EtOH at 60 °C (Scheme 3) without affecting the ester group. The desired unprotected hydrazine was crystallized out and isolated as the benzenesulfonic acid salt (**9**) in pure form (>99% ee) simply by charging heptane.[8]

In conclusion, we have developed an enantioselective hydrogenation of *N*-alkoxycarbonyl hydrazones catalyzed by chiral Rh-complexes. This protocol has been demonstrated at metric ton scale under essentially same conditions with a catalyst loading of as low as 0.2 mol % and has proven to be very practical. The product hydrazines can be used as key building blocks for the syntheses of various heterocycles. The protective group can be chosen from three different options (Boc, methoxycarbonyl, and Cbz), which allow for more flexible elaboration of products.

(6) See Supporting Information for detail.
(7) Tappe, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 91.
(8) The residual Rh in the isolated product was less than 50 ppm.

Scheme 3. Selective Deprotection of the *N*-Protective Group in the Presence of Ester



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Supporting Information Available: Experimental procedures for hydrazone preparation, hydrogenation reactions and deprotection along with characterization data for hydrazones (**4**), hydrogenation products (**5**), and deprotected hydrazine (**9**). This material is available free of charge via the Internet at http://pubs.acs.org.

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