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Highly Enantioselective Hydrogenation of β-Ketoenamides with the Rh-ZhangPhos Catalyst

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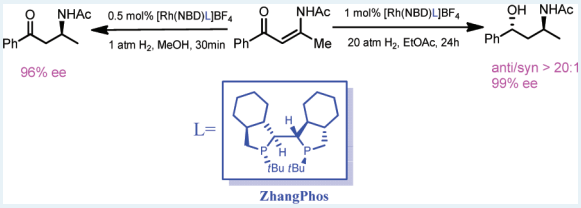
Supporting Information

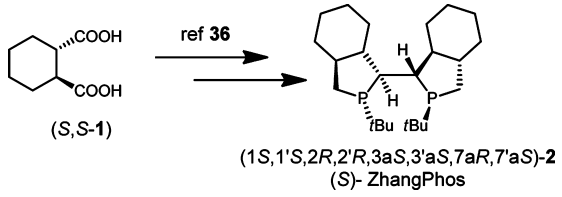
ABSTRACT: A series of β-ketoenamides have been successfully synthesized and applied in the enantioselective hydrogenation with the Rh-ZhangPhos catalyst. This methodology provides an efficient access to a variety of optically active β-amino ketones with up to 99% enantiomeric excess (*ee*). β-Amino ketones can be converted to chiral γ-arylamines in one step without loss of enantioselectivity. Furthermore, direct hydrogenation of β-ketoenamide to chiral 1,3-amino alcohol is also tested with extremely high enantioselectivity and diastereoselectivity.



KEYWORDS: *asymmetric catalysis, enantioselectivity, hydrogenation, phosphine ligand, β-ketoenamides*

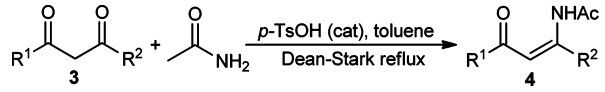
The synthesis of β-amino ketones has drawn great attention because of its importance in biomedical research[1−5] and the pharmaceutical industry.[6−10] β-Amino ketones can also serve as key precursors for the synthesis of amino alcohols,[11−14] 1,3-diamines,[15−17] and β-amino acids. Several stoichiometric and catalytic methods have already been reported for the synthesis of β-amino ketones.[18−22] Notable examples include Lewis acid mediated hetero-Michael addition reactions[23−27] and Mannich-type reactions.[28−31] Asymmetric synthesis of β-amino ketones from sulfinimines was also reported by Davis' group.[32,33] We have reported enantioselective hydrogenation of β-ketoenamides as an efficient way to prepare enantiomerically pure β-amino ketones using the Rh-DuanPhos system.[34,35] Very recently, we reported the design and synthesis of a new electron rich bisphosphine ligand, Zhangphos, which could be synthesized in five steps from commercially available *trans*-1,2-cyclohexanedicarboxylic acid (Scheme 1).[36] Both enantiomers of ZhangPhos are available with asymmetric synthesis. Chiral cyclohexane structure on the backbone is also believed to further increase the electron-donating ability and conformational rigidity of the ligand. Herein, we report a highly enantioselective hydrogenation of β-ketoenamides with the Rh-ZhangPhos catalyst. β-ketoenamides were prepared in one step on multigram scale via direct condensation of readily accessible 1,3-diketones with acetamide (Scheme 2). Only (*Z*)-enamide (**4**) was observed in all cases.[37,38,35]

Scheme 1. Synthesis of ZhangPhos



(1S,1'S,2R,2'R,3aS,3'aS,7aR,7'aS)-**2**
(*S*)- ZhangPhos

Scheme 2. Preparation of β-Ketoenamides



Our initial study began with the hydrogenation of **4a** as the model substrate in MeOH under ambient hydrogen pressure with 0.5 mol % Rh-ZhangPhos complex (Table 1). To our delight, the reaction can be finished within 30 min with complete conversion into chiral β-amino ketone **5a** and with high enantioselectivity (96% enantiomeric excess (*ee*)). Solvent screening revealed that ethanol and isopropanol are also reliable solvents under the same reaction conditions. Aprotic solvents such as toluene and tetrahydrofuran (THF) caused dramatic loss of the reactivity (entry 5 and entry 8). Further increasing hydrogen pressure caused a slight drop in enantioselectivity (entry 11). Lowering the catalyst loading to 0.2 mol % resulted in lower conversion (entry 12).

To further explore the efficiency of the Rh-ZhangPhos catalytic system, we attempted the asymmetric hydrogenation of a series of substrates (**4b−4m**) under the optimized conditions in MeOH (Table 2). All substrates were hydrogenated in full conversions with excellent enantioseletivities. For example, substrates bearing both *para*-substituted electron-

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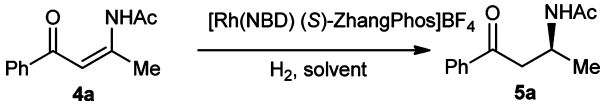
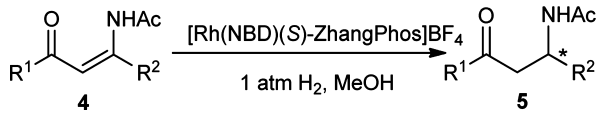
Table 1. Rhodium-Catalyzed Asymmetric Hydrogenation of 4a under Various Conditions



entry[a]	P_{H2}[atm]	solvent	conv. [%][b]	*ee* [%][c]
1	**1.0**	**MeOH**	**>99**	**96**
2	1.0	EtOH	>99	94
3	1.0	^{i}PrOH	>99	95
4	1.0	EtOAc	86	95
5	1.0	toluene	<5	n.d.
6	1.0	CH_2Cl_2	64	96
7	1.0	$ClCH_2CH_2Cl$	13	91
8	1.0	THF	<5	n.d.
9	1.0	1,4-dioxane	35	93
10	2.0	MeOH	>99	96
11	5.0	MeOH	>99	95
12[d]	1.0	MeOH	68	95

[a]Unless otherwise noted, all reactions were carried out with a substrate/catalyst ratio of 200:1 at room temperature for 30 min. [b]Conversions were based on ^{1}H NMR spectroscopy of the crude product. [c]The *ee* value of **5a** was determined by chiral GC analysis. The absolute configuration of **5a** was assigned by comparison of the observed optical rotation with reported data. [d]The reaction was carried out with a substrate/catalyst ratio of 500:1 at room temperature for 30 min.

Table 2. Asymmetric Hydrogenation of 4 with the Rh-ZhangPhos Catalyst

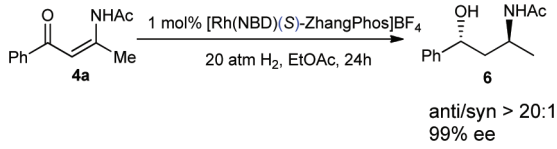


entry[a]	substrate	R^1	R^2	*ee*(%)[b] (config.)[c]
1	**4a**	C_6H_5	Me	96 (S)
2	**4b**	*p*-MeC_6H_4	Me	96 (−)
3	**4c**	*p*-FC_6H_4	Me	98 (−)
4	**4d**	*p*-ClC_6H_4	Me	98 (+)
5	**4e**	*p*-BrC_6H_4	Me	97 (+)
6	**4f**	*p*-$MeOC_6H_4$	Me	98 (+)
7	**4g**	*p*-$^{t}BuC_6H_4$	Me	96 (−)
8	**4h**	*p*-CyC_6H_4	Me	95 (−)
9	**4i**	*m*-MeC_6H_4	Me	98 (−)
10	**4j**	2-thienyl	Me	99 (+)
11	**4k**	2-naphthyl	Me	93 (−)
12	**4l**	Me	Me	99 (−)
13[d]	**4m**	C_6H_5	Et	90 (−)

[a]Unless otherwise noted, all reactions were carried out with a substrate/catalyst ratio of 200:1 in MeOH at room temperature under 1 atm of H_2 for 30 min. In all cases, 100% conversion was observed. [b]Determined by chiral GC or HPLC analysis. [c]The absolute configurations of **5b**-**5m** were not determined. [d]t = 24 h

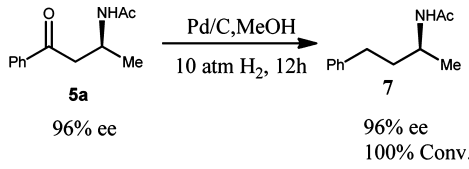
donating and withdrawing groups on the aromatic ring were hydrogenated with uniformly high enantioselectivities (95−98%, entries 2−8). *Meta*-substituted moiety on the aromatic ring further increased the enantioselectivity (entry 9). Substrates with thienyl and naphthyl groups also afforded the hydrogenation products with up to 99% *ee* (entry 10 and 11). A simple aliphatic substrate like **4l** could be hydrogenated under the same reaction conditions with 99% *ee*. However, increasing the steric bulkiness of the R^2 group resulted in significant erosion of the reactivity and enantioselectivity (entry 13). Chiral 1,3-amino alcohol was observed as the hydrogenation product when increasing the hydrogen pressure to 20 atm and reaction time to 24 h. Excellent enantioselectivity and diastereoselectivity were recorded with **4a** as substrate in EtOAc (Scheme 3).

Scheme 3. Synthesis of Chiral 1,3-Amino Alcohol



Chiral *β*-amino ketones such as **5a** could simply be converted to *γ*-arylamine by Pd/C-catalyzed hydrogenation without loss of enantioselectivity (Scheme 4).[39−43] This transformation provided an reliable catalytic approach to chiral *γ*-arylamines, which is highly pharmaceutically and biologically valuable.[44−48]

Scheme 4. Synthesis of Chiral *γ*-Arylamine



In conclusion, we have developed an efficient enantioselective hydrogenation of a wide range of *β*-ketoenamides using the Rh-ZhangPhos catalyst system. This method provided an efficient access to a variety of optically active *β*-amino ketones with excellent enantioselectivities. Further reduction of *β*-amino ketones could give a variety of protected chiral *γ*-aryl amines.

EXPERIMENTAL SECTION

General Procedure for the Substrate Preparation. A toluene solution (150 mL) of substituted 1,3-diketone (50 mmol), acetamide (250 mmol), and a catalytic amount of *p*-TsOH (10 mmol) was charged in a Dean−Stark apparatus and refluxed for 24 h. After the solution was cooled down to room temperature, the solvent was evaporated, and the concentrated mixture was passed through a flash chromatography column filled with silica gel (eluent: EtOAc/hexane). The product **4** was collected as a stable crystalline solid.

Preparation of Rh-ZhangPhos Complex [Rh(NBD)-ZhangPhos]BF_4. To a solution of $[Rh(NBD)_2]BF_4$ (67.3 mg, 0.18 mmol) in degassed THF (1 mL) at −10 °C was added a solution of (**1*S*,1′*S*,2*R*,2′*R*,3a*S*,3′a*S*,7a*S*,7′a*S*)-2** (ZhangPhos) (74.6 mg, 0.189 mmol) in THF (2 mL). The resulting red solution was allowed to warm to room temperature and stirred for 15 min. The solution was concentrated to about 1 mL and then was added degassed Et_2O (12 mL) under vigorous stirring. The resulting precipitate was filtered, further washed with ether (3 × 10 mL) for three times, and dried under vacuum to afford a brown solid (79.1 mg, 65%).

General Procedure for the Asymmetric Hydrogenation. In a glovebox filled with nitrogen, [Rh(NBD)-ZhangPhos]BF_4 complex (6.7 mg, 0.01 mmol) was dissolved in corresponding solvent (10 mL). To 1 mL of this solution, the substrate (0.2 mmol for 0.5 mol % catalyst loading) was

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added. The resulting solution was then transferred into an autoclave and charged with hydrogen. The hydrogenation was performed at room temperature for 30 min. After carefully releasing the pressure in hood, the reaction mixture was passed through a short silica-gel plug to remove the catalyst. Enantiomeric excess were determined with the resulting solution by chiral GC or HPLC.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Further details on the NMR characterization and enantioselectivity analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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