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Enantioselective Synthesis of Optically Pure β-Amino Ketones and γ-Aryl Amines by Rh-Catalyzed Asymmetric Hydrogenation

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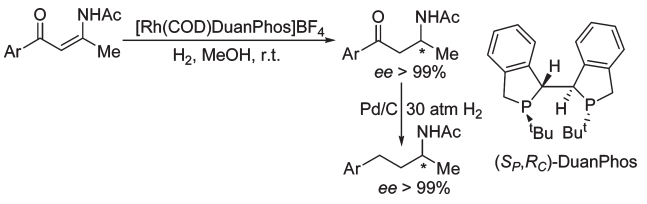
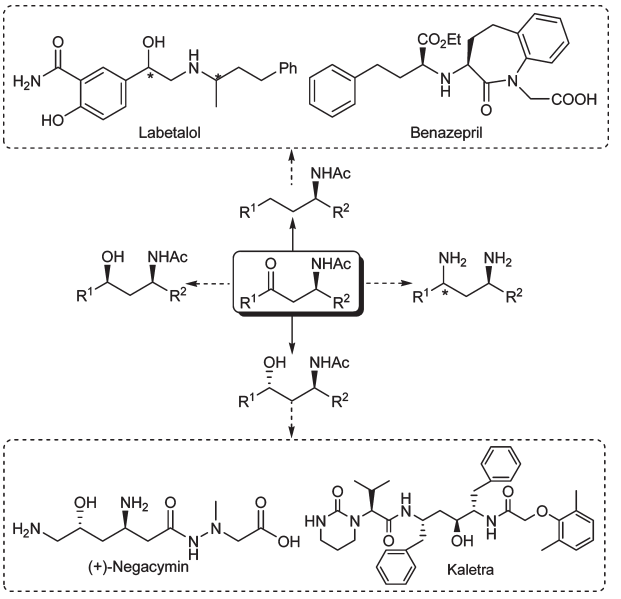


A series of optically pure β-amino ketones have been synthesized in high enantioselectivities (ee > 99%) by Rh-DuanPhos-catalyzed asymmetric hydrogenation of readily prepared β-keto enamides. Further reduction of these β-amino ketones with hydrogen and Pd/C leads to the formation of a variety of protected enantiomerically pure γ-aryl amines (ee > 99%), which are key building blocks in many bioactive molecules.

Enantiomerically pure β-amino ketones are useful bifunctional intermediates for the synthesis of many biologically active molecules.[1] Specifically, these amino ketones can serve as key precursors of *syn*- and *anti*-1,3-amino alcohols,[2] γ-aryl amines,[3] and *syn*- and *anti*-1,3-diamines.[4] Some important pharmaceutical products bearing these functionalities[5] are illustrated in Scheme 1.

SCHEME 1. Potential Applications of Optically Pure β-Amino Ketones



The development of an efficient synthesis of β-amino ketones has received considerable attention in the last decades. Various protocols have been developed to synthesize racemic β-amino ketones,[6] such as Lewis acid mediated hetero-Michael addition reaction[7] and the Mannich reaction.[8] Recently, a stoichiometric

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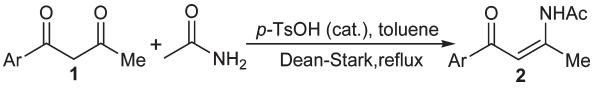
SCHEME 2. Preparation of β-Keto Enamides

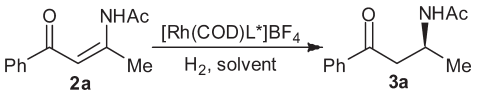


transformation was reported by Davis' group, which featured effective preparation of optically pure β-amino ketones from a Weinreb amide.[9] Hsiao's group discovered a highly efficient method to synthesize β-amino acid derivatives by asymmetric hydrogenation of unprotected β-enamino esters and amides using commercially available ligands under mild conditions.[10] To the best of our knowledge, there is no research involved the synthesis of optically pure β-amino ketones through catalytic asymmetric hydrogenation. Herein, we present a Rh-catalyzed highly enantioselective hydrogenation of β-keto enamides as an efficient way to prepare enantiomerically pure β-amino ketones and their derivatives, γ-aryl amines. Our method has the following advantages: (a) Starting materials **1** and substrates **2** can be readily prepared in high yields (Scheme 2). (b) A series of optically pure β-amino ketones can be synthesized in high ee's through asymmetric hydrogenation.[11] (c) Enantiomerically pure β-amino ketones can be easily converted to many useful products.

A series of well-defined β-keto enamides were prepared by direct condensation of readily accessible 1,3-diketones[12] with an acetamide under a Dean−Stark condition (Scheme 2).[13] The desired substrates **2a**−**o** were obtained in moderate to good yield (up to 90%) as stable crystalline solids. Only *Z* enamide was observed in all cases because of the presence of intramolecular hydrogen bonding.

Initial evaluation of the hydrogenation of **2a** was carried out with Rh-DuanPhos (L1) catalyst[14a] in EtOAc under ambient hydrogen pressure. We obtained good conversion and excellent enantioselectivity to the desired product **3a** (Table 1, entry 1). Further examination of the solvent effect revealed that the reaction was solvent dependent, and polar solvents improved its performance dramatically (entries 2−10). In contrast, the highest conversion and enantioselectivity were achieved in MeOH (entry 10). Several commercial available ligands including Et-DuPhos (L2),[14b] Me-DuPhos (L3),[14b] *f*-binaphane (L4),[14c] binapine (L5),[14d] C_3-TunePhos (L6),[14e] and BINAP (L7)[14f] were screened for the hydrogenation of **2a** (Figure 1), and only DuanPhos, a highly rigid electron-donating P-chiral bisphospholane ligand developed by our group, offered the best result (entries 11−16 vs entry10).

TABLE 1. Rhodium-Catalyzed Asymmetric Hydrogenation of 2a under Various Conditions[a]



entry	L*	P_{H2} (atm)	solvent	conv[b] (%)	ee[c] (%)
1	L1	1.0	EtOAc	89	98
2	L1	1.0	toluene	2.0	>99
3	L1	1.0	CH_2Cl_2	46	94
4	L1	1.0	THF	2.0	>99
5	L1	1.0	1,4-dioxane	34	98
6	L1	1.0	EtOH	>99	95
7	L1	1.0	$ClCH_2CH_2Cl$	0.2	99
8	L1	1.0	^{i}PrOH	>99	95
9	L1	1.0	CF_3CH_2OH	30	64
10	**L1**	**1.0**	**MeOH**	**>99**	**96**
11	L2	1.0	MeOH	16	87
12	L3	1.0	MeOH	0.2	98
13	L4	1.0	MeOH	15	37
14	L5	1.0	MeOH	3.0	94
15	L6	1.0	MeOH	0.1	89
16	L7	1.0	MeOH	0.3	3.0
17	L1	1.5	MeOH	>99	95
18	L1	2.0	MeOH	>99	94
19	L1	5.0	MeOH	>99	91

[a]All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature for 20 min. [b]Conversions were based on ^{1}H NMR spectroscopy of the crude product. [c]Determined by chiral GC analysis. The absolute configuration of **3a** was assigned by comparison of the observed optical rotation with reported data.

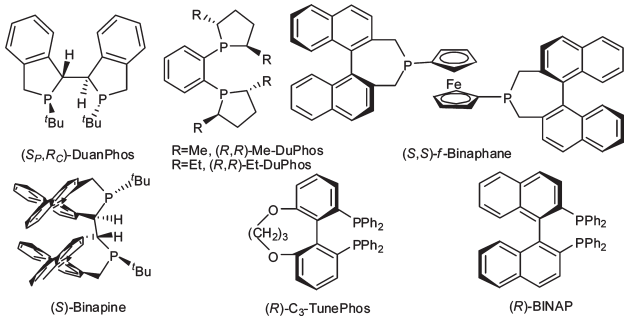


FIGURE 1. Chiral ligands for asymmetric hydrogenation.

Increasing hydrogen pressure caused a slight drop in enantioselectivities (entries 17−19).

To further explore the efficiency and the applicability of the Rh-DuanPhos catalytic system, we investigated the asymmetric hydrogenation of a variety of substrates, **2b**−**o**, under the optimized conditions (Table 1, entry 10). To our delight, all substrates were hydrogenated in full conversions with good to excellent enantioselectivities (Table 2). Compared with **2a**, electron-donating groups or electron-withdrawing groups at the *para* position of the phenyl moiety had no appreciable effect on the enantioselectivities (95−99% ee, entries 2−8). Moving the methyl group to the *meta* position increased the enantioselectivity to 99% (entry 9), while the *ortho* methyl group decreased the enantioselectivity to 87% (entry 10). It is probable that the *ortho* substituents interfere with the preferred coordination of the C=C bond to the metal center and lead to lower facial selectivity. Asymmetric hydrogenation of substrates bearing other aromatic rings, such as **2k** and **2l**, afforded the corresponding products with 99% and 95% ee, respectively (entries 11 and 12). The enantioselectivities

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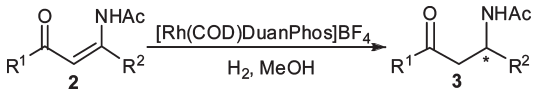
TABLE 2. Asymmetric Hydrogenation of 2 with the Rh-DuanPhos Catalytic System[a]



entry	2	R^1	R^2	3	ee[b,c] (%)
1	**2a**	C_6H_5	Me	**3a**	96 (*S*)
2	**2b**	*p*-MeC_6H_4	Me	**3b**	97
3	**2c**	*p*-$MeOC_6H_4$	Me	**3c**	97
4	**2d**	*p*-FC_6H_4	Me	**3d**	98
5	**2e**	*p*-ClC_6H_4	Me	**3e**	98
6	**2f**	*p*-BrC_6H_4	Me	**3f**	95
7	**2g**	*p*-^{t}BuC_6H_4	Me	**3g**	96
8	**2h**	*p*-CyC_6H_4	Me	**3h**	95
9	**2i**	*m*-MeC_6H_4	Me	**3i**	99
10[d]	**2j**	*o*-MeC_6H_4	Me	**3j**	87
11	**2k**	2-thienyl	Me	**3k**	99
12	**2l**	2-naphthyl	Me	**3l**	95
13[e]	**2m**	C_6H_5	Et	**3m**	89
14[f]	**2n**	C_6H_4	CO_2Et	**3n**	81(*S*)
15	**2o**	Me	Me	**3o**	> 99

[a]All reactions were carried out with a substrate/catalyst ratio of 100:1 in MeOH at room temperature under 1 atm of H_2 for 20 min. In all cases, 100% conversion was observed. [b]Determined by chiral GC or HPLC analysis. [c]The absolute configurations of **3a** and **3n** were assigned by comparison of the observed optical rotation with reported data. [d]2.5 h. [e]24 h. [f]30 °C, 60 atm of H_2, 12 h.

decreased from 96% to 81% when the steric bulkiness of R^2 was increased from methyl to ethyl or ethyl ester group (entry 1 vs entries 13 and 14). It was noteworthy that the hydrogenation of **2o** gave ee > 99% (entry 15) when R^1 was changed from an aryl group to a methyl group. The best outcome may be attributed to the decreased steric hindrance enhancing the coordination of enamide to rhodium.

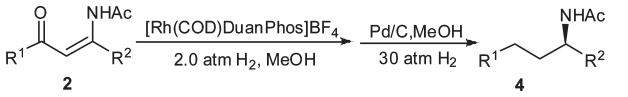
It is known that Pd/C-catalyzed hydrogenation has the ability to remove the carbonyl oxygen from the aromatic ketone derivatives,[15] and we applied this method to the reduction of optically pure β-amino arylketones to optically pure γ-aryl amines. In a one-pot reaction, we first reduced β-keto enamides with Rh-DuanPhos followed by Pd/C hydrogenolysis. As shown in Table 3, a range of enantiomerically pure γ-aryl amines were prepared in full conversions with good to excellent ee values.

In summary, a series of optically pure β-amino ketones have been synthesized with high ee values by asymmetric hydrogenation of readily prepared β-keto enamides using Rh-DuanPhos catalyst. Subsequent reduction of these β-amino ketones with hydrogen and Pd/C leads to the formation of a variety of protected enantiomerically pure γ-aryl amines. Our strategy therefore represents an efficient and novel catalytic approach to prepare these two kinds of pharmaceutically and biologically valuable compounds.

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 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 **2** was collected as a stable crystalline solid.

TABLE 3. Synthesis of γ-Aryl Amines 4 via One-Pot Asymmetric Reduction[a]



entry	2	R^1	R^2	4	ee[b,c] (%)
1	**2a**	C_6H_5	Me	**4a**	97 (*S*)
2	**2b**	*p*-MeC_6H_4	Me	**4b**	95
3	**2c**	*p*-$MeOC_6H_4$	Me	**4c**	> 99
4	**2d**	*p*-FC_6H_4	Me	**4d**	96
5	**2g**	*p*-^{t}BuC_6H_4	Me	**4g**	96
6	**2h**	*p*-CyC_6H_4	Me	**4h**	96
7	**2i**	*m*-MeC_6H_4	Me	**4i**	97
8	**2j**	*o*-MeC_6H_4	Me	**4j**	89
9	**2m**	C_6H_5	Et	**4m**	94 (*S*)
10[d]	**2n**	C_6H_5	CO_2Et	**4n**	79 (*S*)

[a]All reactions were carried out with a substrate/DuanPhos ratio of 100:1 in MeOH at room temperature for 1 h, while the ratio of substrate to Pd/C is 10:1. In all cases, 100% conversion was observed. [b]Determined by chiral HPLC analysis. [c]The absolute configurations of **4a**, **4m**, and **4n** were assigned by comparison of the observed optical rotation with reported data. [d]The first hydrogenation was performed at 30 °C under 60 atm of H_2 for 12 h.

General Procedure for the Asymmetirc Hydrogenation. A stock solution of $[Rh(COD)_2]BF_4$ (COD = cycloocta-1,5-diene) and DuanPhos at a 1:1.1 molar ratio was stirred in MeOH at room temperature for 30 min in a nitrogen-filled glovebox. The required amount of catalyst solution (0.1 mL, 0.001 mmol) was then transferred by syringe into the vials charged with different substrates (0.1 mmol for each) in MeOH (2.9 mL). All of the vials were placed together in a steel autoclave into which hydrogen gas was charged. After the solution was stirred at room temperature for 20 min, the hydrogen was released slowly, the solution was concentrated, and then the crude product was eluted by EtOAc through a plug of silica gel to remove the metal complex. The purified product mixture was analyzed by chiral GC or HPLC to determine the ee value.

3a:[16] 96.2% ee; enantiomeric excess was determined by GC, chiral Beta Dex 390 column, 160 °C, 1.0 mL/min, t_{major} = 72.9 min, t_{minor} = 76.1 min; $[\alpha]^{20}_D$ = −6.9 (*c* = 1.0, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90−7.88 (m, 2H), 7.51−7.49-(m,1H), 7.42−7.38 (m, 2H), 6.26 (br, 1H), 4.43−4.37 (m, 1H), 3.31−3.26 (dd, *J* = 4.4, 16.8 Hz, 1H), 3.04−2.98 (dd, *J* = 6.0, 16.8 Hz,1H), 1.89 (s, 3H), 1.23−1.22 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.3, 169.5, 136.9, 133.5, 128.7, 128.1, 43.4, 42.6, 23.4, 20.0.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and analysis of enantioselectivities of hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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