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Efficient Rhodium-Catalyzed Asymmetric Hydrogenation for the Synthesis of a New Class of *N*-Aryl β-Amino Acid Derivatives

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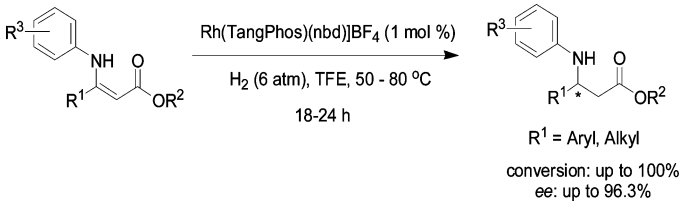
ABSTRACT



***N*-Aryl β-amino esters were obtained by asymmetric hydrogenation of a new class of *N*-aryl β-enamino esters. High conversions and up to 96.3% ee values were achieved with a Rh-TangPhos catalyst.**

Enantiomerically pure β-amino acids and their derivatives are very important chiral building blocks for the synthesis of β-peptides, β-lactams, and many important biologically active compounds.[1] Among the stoichiometric and catalytic methods for β-amino acids synthesis, asymmetric hydrogenation is one of the most atom economic and efficient approaches.[2] Most of the current approaches require an acyl protecting group on the nitrogen of the unsaturated β-amino acids as a chelating group to achieve high reactivities and enantioselectivities.[3] A major drawback to these approaches is the difficulty of introducing and removing this protecting group, which limits their potential applications.[4] *N*-Aryl β-amino acid derivatives are key structural elements of many natural products and drug intermediates.[5,6] We envision that the most efficient way to prepare such compounds is to perform asymmetric hydrogenation of *N*-aryl β-enamino esters (Figure 1). For examples, the most efficient way to introduce a phenyl group on drug CGP-68730A is the enantioselective hydrogenation of *N*-aryl β-enamine (Figure 1, route a). It is very difficult to couple two pieces, which contain phenyl moiety and amine moiety respectively, together as shown below (Figure 1, route b). Although the aryl group can be introduced by the transition metal-catalyzed amination reaction (Figure 1, route d), the more direct method is to prepare *N*-aryl β-enamine and perform asymmetric hydrogenation (Figure 1, route c). To the best of our

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(5) For previous examples of asymmetric hydrogenation of electron-rich *N*-alkyl and *N*,*N*-dialkyl enamines, see: (a) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985. (b) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2000**, *41*, 2351.

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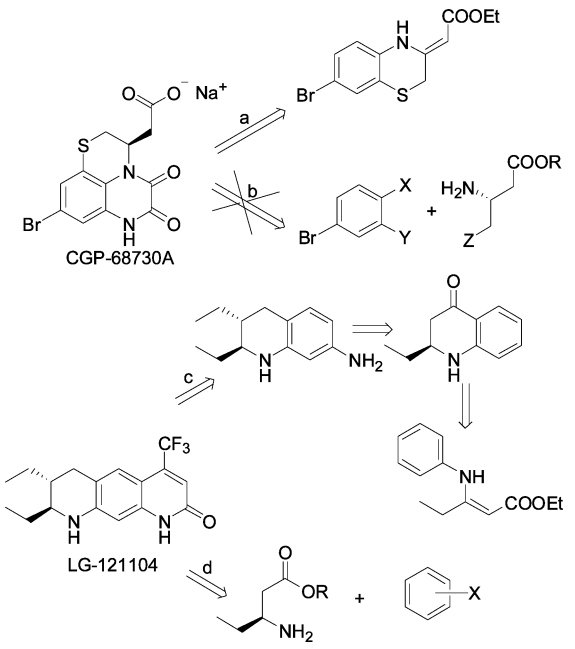


Figure 1. Examples of drug candidates and potential substrates for hydrogenation.

knowledge, only the Merck group reported the synthesis of β-amino acids via asymmetric hydrogenation of unprotected enamines.[7] There have been no reports on the asymmetric hydrogenation of *N*-aryl β-enamine. Herein, we report a highly enantioselective hydrogenation of *N*-aryl β-enamino esters by using rhodium complexes with the electron-donating bisphosphines developed in our lab (e.g. TangPhos,[8a] DuanPhos,[8b] and Binapine[2e]).

A family of enamines has been prepared from β-keto esters and aniline derivatives (Figure 2).[9] These compounds are

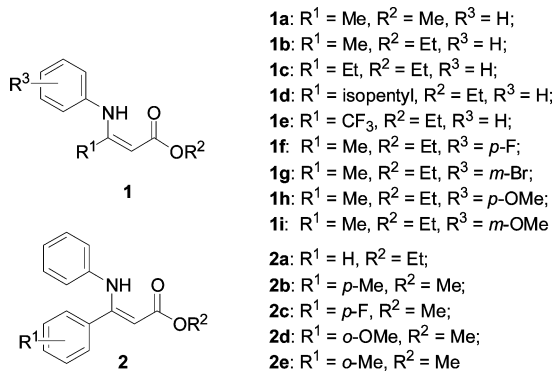


Figure 2. Structure of substrates **1** and **2**.

obtained exclusively as (*Z*)-isomers according to literature procedures.[9,10]

(7) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.

To explore the asymmetric hydrogenation reaction, substrate **1a** was employed in the screening of reaction conditions with several ligand systems (Figure 3). Surprisingly,

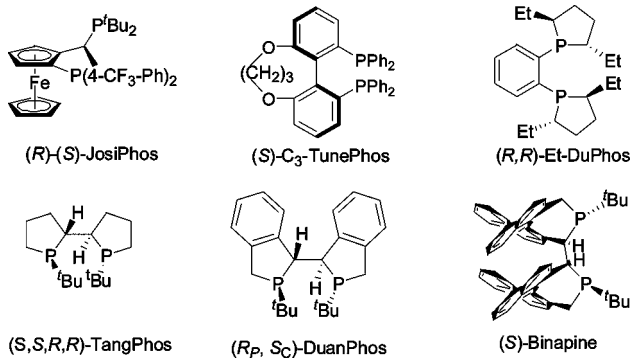
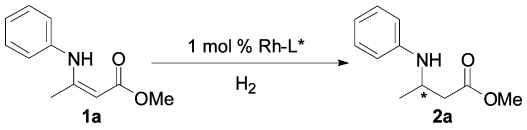


Figure 3. Structure of ligands for asymmetric hydrogenation.

poor enantioselectivity (31.9% ee) was obtained for a JosiPhos ligand (Table 1, entry 1), which was effective for

Table 1. Asymmetric Hydrogenation of Substrate **1a**



entry	catalyst[a]	solvent	*T*, °C	$P(H_2)$, atm	conv,[b] %	ee,[c] %	config[d]
1	**3a**	TFE	50	6	100	31.9	(−)
2	**3b**	MeOH	50	6	67	76.7	(+)
3	**3c**	MeOH	50	6	52	47.9	(−)
4	**3d**	MeOH	50	6	95	76.1	(−)
5	**3d**	CH_2Cl_2	50	6	77	94.6	(−)
6	**3d**	TFE	50	6	100	90.9	(−)
7	**3d**	TFE	rt	6	67	92.9	(−)
8	**3d**	TFE	rt	30	83	77.7	(−)
9	**3d**	TFE	rt	95	75	72.9	(−)
10	**3e**	TFE	50	6	78	69.6	(−)
11	**3f**	TFE	50	6	58	50.1	(+)

[a] **3a**: (*R*)-(*S*)-JosiPhos/[Rh(cod)Cl]$_2$. **3b**: [Rh(*S*)-C_3-TunePhos(cod)]BF_4. **3c**: [Rh(*R*,*R*)-Et-DuPhos(cod)]BF_4. **3d**: [Rh(*S*,*S*,*R*,*R*)TangPhos(nbd)]SbF_6. **3e**: [Rh(R_P,S_C)DuanPhos(nbd)]SbF_6. **3f**: [Rh(*S*)-Binapine(cod)]BF_4. [b] Assayed by NMR. [c] Assayed by chiral HPLC. [d] Absolute configurations were not determined.

hydrogenation of unprotected β-enamine.[7] While chiral biaryl bisphosphine (*S*)-C_3-TunePhos[11] offered moderate conversion

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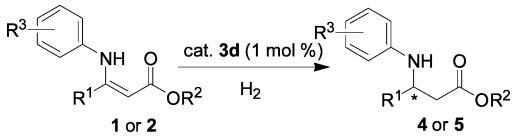
and enantioselectivity (Table 1, entry 2), higher conversion was achieved with a more electron-donating trialkyl-bisphosphine TangPhos (Table 1, entry 4). (*R*,*R*)-Et-DuPhos was also tested, which gave only 47.9% ee and 52% conversion (Table 1, entry 3). We also screened several solvents for the reaction (Table 1, entries 4−6). TFE (2,2,2-trifluoroethanol) was found to be the optimal solvent for achieving both high conversions and ee values (Table 1, entry 6). Interestingly, we also found that there is a strong pressure effect for this reaction (Table 1, entries 7−9). Increasing reaction pressure led to the decrease of the enantioselectivities. Compared with the results achieved by TangPhos (Table 1, entry 6), lower conversions and ee values were obtained with DuanPhos (Table 1, entry 10) and Binapine (Table 1, entry 11).

Using the optimized reaction condition for hydrogenation of **1a** (Table 1, entry 6), we next examined a variety of *N*-aryl β-alkyl enamino esters (Table 2, entries 2−9). Over 90% ee values were obtained for most of the substrates. Increasing the steric hindrance of the R^1 group resulted in a decrease of ee (Table 2, entry 4). Low conversion and enantioselectivity were observed for substrate **1e**, which has an electron-withdrawing group (Table 2, entry 5). While the reaction condition (Table 1, entry 6) was good for hydrogenation of *N*-aryl β-alkyl enamines, only 90.9% ee and low conversion (30%) were obtained when *N*-aryl β-aryl enamine **2b** was used. To address the reactivity issue, we increased the reaction temperature to 80 °C and complete conversion and 91.1% ee were achieved (Table 2, entry 11). For hydrogenation of *N*-aryl β-aryl enamines **2** (Table 2, entries 10−14), introduction of an electron-withdrawing group on the β-aryl group resulted in higher enantioselectivity (Table 2, entry 12). Substrates with ortho-substituted electron-donating β-aryl groups led to much lower ee values and reactivities (Table 2, entries 13 and 14).

In conclusion, we have developed a highly efficient method for the synthesis of a new class of *N*-aryl substituted β-amino acid derivatives. The reaction is highly substrate dependent. Introduction of a highly electron-donating trialkyl phosphine ligand TangPhos is critical for achieving high conversion and enantioselectivity. This method is potentially useful for the preparation of a number of chiral drug intermediates. Further investigation will be reported in due course.

Table 2. Asymmetric Hydrogenation of Substrates **1a**−**i**[a] and **2a**−**e**[b]



entry	substrate	conv,[c] %	ee,[d] %	config[e]
1	**1a**	100	90.9	(−)
2	**1b**	100	94.8	(−)
3	**1c**	100	94.9	(+)
4	**1d**	100	89.7	(+)
5	**1e**	48	78.9	(+)
6	**1f**	100	96.3	(−)
7	**1g**	83	96.1	(−)
8	**1h**	78	93.8	*R*[f]
9	**1i**	88	95.7	(−)
10	**2a**	100	92.3	(−)
11	**2b**	100	91.1	(−)
12	**2c**	100	95.3	(+)
13	**2d**	100	89.7	(−)
14	**2e**	67	79.3	(+)

[a] Reaction conditions: 1 mol % of **3d**, 50 °C, 6 atm of H_2, 18 h. [b] Reaction conditions: 1 mol % of **3d**, 80 °C, 6 atm of H_2, 24 h. [c] Assayed by NMR. [d] Assayed by chiral HPLC. [e] Absolute configurations were not determined. [f] Absolute configuration was determined by comparison of the sign of the optical rotation with the reported data (see the Supporting Information).

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Supporting Information Available: General procedure for the synthesis of *N*-aryl β-enamino esters and their hydrogenations and physical characterization data for substrates and hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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