Synthesis of Melatonin Receptor Agonist Ramelteon via Rh-catalyzed Asymmetric Hydrogenation of an Allylamine

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In the course of developing a practical synthetic method for the selective melatonin MT1/MT2 receptor agonist Ramelteon, a rhodium Josiphos complex was found to be an excellent catalyst for asymmetric hydrogenation of the key precursor, allylamine **1**.

Ramelteon[1,2f] [(*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide] (Figure 1), effective in the treatment of circadian rhythm sleep disorders, consists of a unique three-fused-ring system with an asymmetric center at the benzylic position (C8). We have previously reported a practical synthesis of Ramelteon based on a ruthenium-catalyzed asymmetric hydrogenation, in which the acylamino moiety of the substrate **1** might play an important role as an anchoring group to realize the excellent enantioselectivity.[1c]

A great deal of effort has been made to develop efficient and potent chiral ligands in the field of asymmetric hydrogenation.[2] Among those chiral ligands, ferrocene-based diphosphines, especially Josiphos ligands enjoy a broad range of applications[3] due to their high reactivity and diversity that offers differing steric and electronic properties. The fact that the Josiphos type ligand has been utilized for the economical manufacture of (*S*)-metolachlor, also encouraged us to investigate its performance. In the course of exploring novel catalysts for the synthesis of Ramelteon, we investigated the use of the Josiphos family of ligands with the allylamine **1**, which is a straightforward substrate[4] for asymmetric hydrogenation. Precatalysts of Rh-Josiphos were prepared in situ from 2 mol % of $[Rh(cod)Cl]_2$ and each ligand in MeOH at room temperature.[5] We started by using the most widely utilized ligand, Josiphos **3a**, and surprisingly found that the reaction proceeded very smoothly even under 0.7 MPa of H_2 at room temperature, to afford compound **2** in quantitative yield with 74% ee (Table 1, Entry 1). To the best of our knowledge, this is the first asymmetric hydrogenation of an allylamine using Rh-Josiphos catalysts.[4]

Josiphos ligands have two sets of tunable substituents on the phosphorous atoms. Among the ligands tested (**3b**–**3n**), ligand **3k** gave the best result, with satisfactory enantioselectivity (Table 1, Entry 11). Consideration of the differences between the ligands **3a**–**3n** and the outcome of the reaction, can give some clues to further understanding of the Joshiphos ligands. All ligands listed preferably gave the identical stereoisomer.

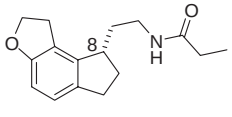
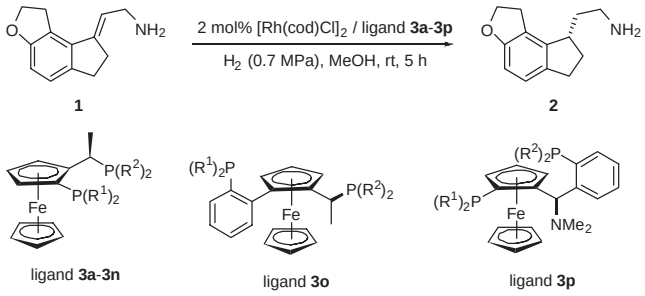


Figure 1. Structure of Ramelteon.

Table 1. Asymmetric hydrogenation of compound **1**[a]



Entry	Ligand	R^1 [b]	R^2	ee/%[c]	yield/%[c]
1	**3a**	C_6H_5	*c*-Hex	74	>99
2	**3b**	4-MeO-Xyl	*c*-Hex	73	95
3	**3c**	3,5-$(CF_3)_2C_6H_3$	*c*-Hex	35	57
4	**3d**	4-$CF_3C_6H_4$	*c*-Hex	78	93
5	**3e**	C_6H_5	*t*-Bu	14	91
6	**3f**	4-MeO-Xyl	*t*-Bu	43	87
7	**3g**	3,5-$(CF_3)_2C_6H_3$	*t*-Bu	49	89
8	**3h**	4-$CF_3C_6H_4$	*t*-Bu	42	96
9	**3i**	4-F-C_6H_4	*t*-Bu	34	92
10	**3j**	4-MeO-C_6H_4	*t*-Bu	10	93
11	**3k**	2-Furyl	*t*-Bu	92	95
12	**3l**	2-Furyl	Xyl	27	32
13	**3m**	*c*-Hex	C_6H_5	23	86
14	**3n**	4-MeO-Xyl	Xyl	50	79
15	**3o**	C_6H_5	*c*-Hex	80	92
16	**3p**	C_6H_5	C_6H_5	77	93

[a]The reaction was conducted on a 0.1 mmol scale at room temperature under 0.7 MPa of H_2. [b]Abbreviations: 4-MeO-Xyl = 4-CH_3O-3,5-$(CH_3)_2C_6H_2$, Xyl = 3,5-$(CH_3)_2C_6H_3$. [c]Determined by HPLC analysis (CHIRALCEL OD-RH column).

The effect of the electronic properties of the R^1 groups on the enantioselectivity was found to be limited. With *c*-Hex as the R^2 group, C_6H_5, 4-MeO-Xyl, and 4-$CF_3C_6H_4$ gave almost identical enantioselectivities (Table 1, Entry 1, 2, and 4). With *t*-Bu as the R^2 group, all substitutions on the R^1 groups also gave low enantioselectivities (Table 1, Entry 5, 6, 7, 8, 9, and 10). The R^1 groups seem to have little effect on enantioselectivity, except for the furyl group, where drastic improvement was observed and the best ee was obtained.

The furyl group is unique and outstanding as a substituent. It has been generally recognized that 2-Furyl phosphines are poor σ-donor ligands and useful ligands for asymmetric reactions and transition metal-catalyzed reactions such as the Stille reaction.[6] Therefore, we anticipated that the ligand having a 2-furyl substituent might lead to substantial change in the complex.

The bulkiness of the R^2 group may have a weak correlation to the enantioselectivities. With 4-MeO-Xyl as the R^1 group,

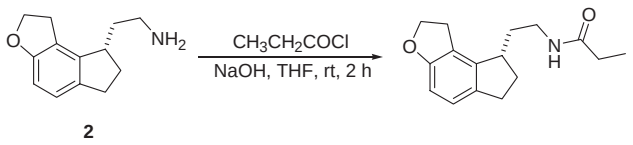


Figure 2. Synthesis of Ramelteon.

c-Hex as the R^2 group gave good enantioselectivity of 73% ee, followed by Xyl (50% ee) and *t*-Bu (43% ee) (Table 1, Entry 2, 14, and 6). Also, with 2-Furyl as the R^1 group, *t*-Bu (92% ee) was superior to Xyl (27% ee) as the R^2 group (Table 1, Entry 11 and 12). Thus the structural tunability[3d,3e] of the Joshiphos ligand family has allowed us to find a series of effective ligands with optimal bite angle and electronic properties.

Ligands **3o** (Walphos type[7]) and **3p** (Taniaphos type[8]) gave promising enantioselectivities and chemical yields. Optimization of substituents on Walphos and Taniaphos type ligands are expected to give satisfactory yields and enantiomeric excesses.

Subsequently, compound **2** was successfully converted to Ramelteon by treatment of propanoyl chloride to confirm that the conversion is free from racemization. (Figure 2)

In addition to the satisfactory enantioselectivities obtained, the finding that primary amino groups may act as an anchoring group to the rhodium atom could be beneficial for the asymmetric hydrogenation of olefins having primary amino groups.

In conclusion, a highly enantioselective hydrogenation of the allylamine **1** catalyzed by Rh-Josiphos has been developed. The procedure is suitable for the preparation of Ramelteon owing to the excellent enantiomer excess and low hydrogen pressure.

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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5 Experiments were carried out under argon atmosphere by standard Schlenk techniques (Table 1, Entry 11). To a solution of [(2*E*)-2-(1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-ylidene)ethyl]amine (**1**) (20 mg, 0.1 mmol) in methanol (0.5 mL) in a glass autoclave was added a solution of (*R*)-1-[(*S*)-2-(di-2-furylphosphino)ferrocenyl]ethyldi(*tert*-butyl)phosphine (ligand **3k**, 2.7 mg, 1.3 equiv to Rh) and $[Rh(cod)Cl]_2$ (1.0 mg, s/c = 25) in methanol (0.5 mL) by cannula. Hydrogen (0.7 MPa) was introduced, and the reaction mixture was stirred at room temperature. After 5 h, enantiomeric excess (92%) and chemical yield (95%) were determined by HPLC analysis (CHIRALCEL OD-RH, eluted with 0.1 M KPF_6 (pH 2)/acetonitrile = 750/250 (v/v), 0.5 mL/min).

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