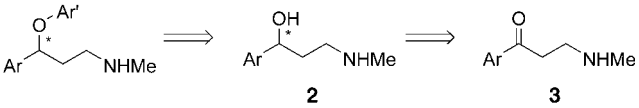
Hydrogenations

Practical Synthesis of Enantiopure γ-Amino Alcohols by Rhodium-Catalyzed Asymmetric Hydrogenation of β-Secondary-Amino Ketones

*Duan Liu, Wenzhong Gao, Chunjiang Wang, and Xumu Zhang**

Enantioselective hydrogenation of amino ketones catalyzed by Ru–[1] or Rh–phosphine[2] complexes provides an efficient method for the synthesis of enantiomerically active amino alcohols, a class of chiral compounds of great importance in pharmaceutical products. A recent challenging target[3] inspired us to look for a practical solution for the enantioselective reduction of β-amino ketones with a secondary amino group, an unsolved class of substrates in asymmetric hydrogenation. To our knowledge, no Ru catalytic system has successfully been used for the asymmetric hydrogenation of amino ketones with a secondary amino group. A Rh–MCCPM (MCCPM = (2*S*,4*S*)-4-dicyclohexylphosphino-2-diphenylphosphinomethyl-1-(*N*-methylcarbamoyl)pyrrolidine) catalyst has been reported for the hydrogenation of one β-secondary-amino ketone substrate with only moderate efficiency (80% *ee*, turnover number (TON) = 1000).[2e] Given the importance of chiral γ-amino alcohols **2** as key intermediates for the synthesis of pharmaceutical products **1**[4] (Scheme 1), an efficient enantioselective reduction of β-secondary-amino ketones **3** into **2** would be of great significance, not only for pharmaceutical development but also as a generally useful organic transformation. Herein, we report a Rh-catalyzed highly efficient hydrogenation of a series of β-secondary-amino ketones with *ee* values of up to > 99% and with turnover numbers of more than 4500; this hydrogenation provides a potentially practical synthesis of key pharmaceutical intermediates.



2 **3**

1a: Ar = Ph, Ar' = 4-CF_3-Ph (fluoxetine)
1b: Ar = Ph, Ar' = 2-Me-Ph (tomoxetine)
1c: Ar = Ph, Ar' = 2-OMe-4-CF_3-Ph (nisoxetine)
1d: Ar = thiophenyl, Ar' = 1-naphthyl (duloxetine)

Scheme 1. A retrosynthesis of fluoxetine and related compounds by asymmetric hydrogenation.

γ-Secondary amino alcohols **2** are of particular interest to synthetic chemists as they are key intermediates for the synthesis of an important class of antidepressants, **1a–d**.[4] Owing to the different biological activities exhibited by individual enantiomers of **1**, a number of enantioselective syntheses of **1**, as well as of **2**, have been developed in recent years.[5] Although highly enantioselective hydrogenation of β-tertiary-amino ketones, catalyzed by a chiral [$RuCl_2$(diphosphine)(1,2-diamine)] complex, provides an effective route for the enantioselective syntheses of **1**,[1c–e] subsequent selective removal of one *N*-methyl group is needed to afford the desired amino alcohols **2**.[5b] A direct hydrogenation of β-secondary-amino ketones **3** would be a more attractive and economic strategy for the syntheses of **2**. However, Ru systems have not been effective for the latter reduction so far. Recently, we revealed the synthesis of a highly electron-donating P-chiral trialkylbisphospholane ligand, **4** (duanphos, see Scheme 2), in both enantiomeric forms.[6] The high reactivities and enantioselectivities observed in the Rh–duanphos-catalyzed hydrogenation of various types of functionalized C=C bonds[6] suggest the feasibility of using the Rh–duanphos system for the reduction of the C=O bond in amino ketones, provided a proper metal–substrate chelate forms through coordination of the nitrogen atom to the metallic center.

[*] D. Liu, W. Gao, C. Wang, Prof. X. Zhang
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802 (USA)
Fax: (+1) 814-865-3292
E-mail: xumu@chem.psu.edu

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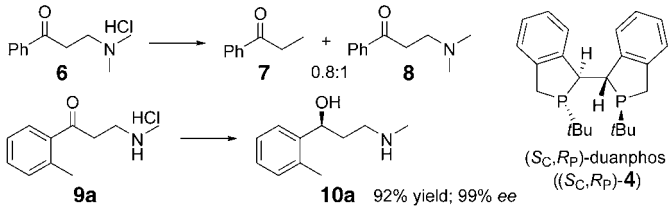
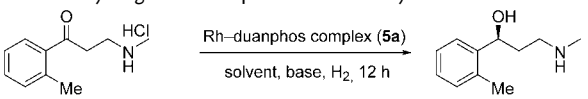


Scheme 2. Asymmetric hydrogenation of β-amino ketone hydrochlorides with [Rh{(S_C,R_P)-**4**}(nbd)]SbF_6 (**5a**) as the catalyst. Reaction conditions: **5a** (0.5 mol%), MeOH, K_2CO_3 (0.5 equiv), H_2 (10 bar), 50°C, 12 h. nbd = norbornadiene.

Initially, the commercially available substrate **6** was examined with [Rh{(S_C,R_P)-**4**}(nbd)]SbF_6 (**5a**) as the catalyst in the presence of K_2CO_3 (0.5 equiv) in MeOH under H_2 (10 bar) at 50°C for 12 h. Unfortunately, none of the desired amino alcohol product was obtained, but a mixture of a deamination byproduct **7**[7] and unconverted free amino ketone **8** was recovered. When isolated **8** was employed without a base under otherwise the same reaction conditions, a similar mixture of **7** and unconverted **8** was obtained. However, we were pleased to find that a β-secondary-amino ketone hydrochloride **9a**[8] was readily hydrogenated to give γ-amino alcohol **10a** in 92% yield with 99% *ee* (<5% deamination byproduct indicated by ^{1}H NMR spectroscopy) after isolation. These observations strongly support our hypothesis that, unlike the situation in the Ru-catalyzed hydrogenation of amino ketones,[1c] an effective ligation of the nitrogen atom to the metallic center to form a metal–substrate chelate is probably critical for achieving high enantioselectivity and reactivity in this hydrogenation. A secondary amino group is a better ligand than a tertiary amino group to coordinate to a Rh center to form a chelate, owing to less steric interaction, and this, in turn, facilitates the reaction rate of C=O bond reduction relative to deamination. Further screening of reaction conditions for the hydrogenation of **9a** (Table 1) resulted in the following observations: 1) A higher temperature or H_2 pressure has little effect on the enantioselectivity but does accelerate the relative rate of hydrogenation, thereby leading to a higher yield of **10a** (Table 1, entries 1–4); 2) although there is no significant solvent effect on the enantioselectivity, the hydrogenation rates differ dramatically with diverse solvents (reflected by the yields of **10a**), and MeOH is found to be the solvent of choice (Table 1, entries 1 and 5–10); 3) both inorganic bases, such as K_2CO_3 and $KHCO_3$, and organic bases, such as triethylamine, can promote the hydrogenation of **9a** with comparable yields and stereoselectivities (Table 1, entries 1, 11, and 12).

Under the conditions optimized for the hydrogenation of **9a**, the hydrogenation of a series of β-secondary-amino ketone hydrochlorides **9a–i** were explored with Rh–complex **5a** and its antipodal complex [Rh{(R_C,S_P)-duanphos}(nbd)]SbF_6 (**5b**). As shown in Table 2, entries 1–7, all the hydrogenations proceeded to completion and afforded the corresponding amino alcohols **10** in high yields (90–93%) with excellent enantioselectivities (93–99% *ee*); these results indicate a high tolerance to the pattern and electronic properties of the substituent on the phenyl ring in terms of

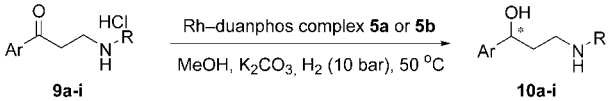
Table 1: Screening of reaction conditions for the Rh-catalyzed asymmetric hydrogenation of β-amino ketone hydrochloride **9a**.[a]



Entry	Solvent[b]	Base	P (H_2) [bar]	T [°C]	Yield [%][c]	*ee* [%][d]
1	MeOH	K_2CO_3	10	50	>95 (92%)	99
2	MeOH	K_2CO_3	50	50	>95	99
3	MeOH	K_2CO_3	2	50	75	98
4	MeOH	K_2CO_3	10	23	95	97
5	EtOH	K_2CO_3	10	50	65	98
6	*i*PrOH	K_2CO_3	10	50	45	94
7	MeCN	K_2CO_3	10	50	50	96
8	CH_2Cl_2	K_2CO_3	10	50	75	94
9	DMF	K_2CO_3	10	50	<10	–
10	THF	K_2CO_3	10	50	<10	–
11	MeOH	$KHCO_3$	10	50	95	98
12	MeOH	NEt_3	10	50	>95	99

[a] The hydrogenations were carried out under the described conditions for each entry with 0.5 mol% of **5a** as the catalyst precursor, according to the general procedure given in the Supporting Information. [b] DMF = *N*,*N*-dimethylformamide. [c] Estimated yields based on ^{1}H NMR spectroscopy of the crude products. The yield after isolation is given in parenthesis. [d] The *ee* values of **10a** were determined by chiral HPLC with an OD-H column after the product had been converted into the *N*-acyl derivative **11a** (see Supporting Information).

Table 2: Rh-catalyzed asymmetric hydrogenation of β-secondary-amino ketone hydrochlorides.[a]

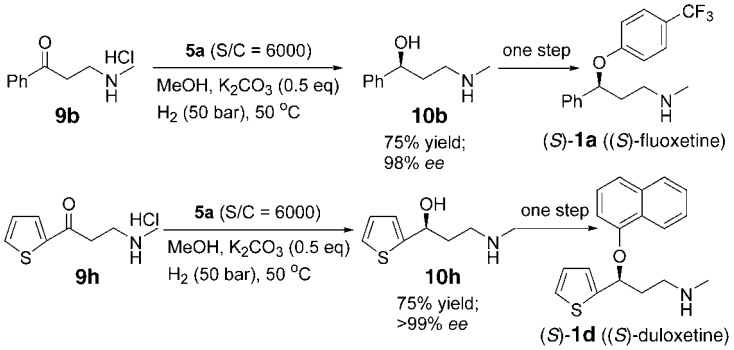


Entry	**9**	Ar	R	Yield [%][b]	*ee* [%]	Configuration[c]
1	**a**	2-Me-phenyl	Me	92	99[d]	*S*
2	**b**	phenyl	Me	90	98[d]	*S*
3	**c**	3-Br-phenyl	Me	90	96[d]	*S*
4	**d**	4-Br-phenyl	Me	93	>99[d]	*S*
5	**e**	2-OMe-phenyl	Me	93	93[d]	*S*
6	**f**	4-OMe-phenyl	Me	93	>99[d]	*S*
7	**g**	2-naphthyl	Me	92	99[e]	*S*
8	**h**	2-thienyl	Me	93	>99[e]	*S*
9	**h**	2-thienyl	Me	93	>99[e]	*R*[f]
10	**i**	phenyl	Bn[g]	90	96[d]	*S*

[a] The hydrogenations were carried out with 0.5 mol% of **5a** (entries 1–8 and 10) or **5b** (entry 9) as the catalyst precursor for 12 h. Complete conversions were indicated by ^{1}H NMR spectroscopy in all runs. See Supporting Information for the general procedure. [b] Yield after isolation. [c] The absolute configurations of **10b** and **10h** were determined by comparing the sign of the optical rotations with reported data. For the other compounds, the absolute configurations were assumed to be *S* when **5a** was used. [d] The *ee* values were determined by chiral HPLC with an OD-H column after the product had been converted into the *N*-acyl derivative (see Supporting Information). [e] The *ee* values were determined directly by chiral HPLC with an OD-H column (see Supporting Information). [f] The Rh complex **5b** was used. [g] Bn = benzyl.

both reactivity and enantioselectivity. In the hydrogenation of a more interesting amino ketone, **9h**, with a heteroaromatic function, (*S*)-**10h** and (*R*)-**10h** were obtained in 93% yield with >99% *ee* by using **5a** and **5b** as the catalyst, respectively (Table 2, entries 8 and 9). An *N*-benzyl-amino ketone, **9i**, was also hydrogenated to afford amino alcohol **10i** in 90% yield and 96% *ee* (Table 2, entry 10).

To demonstrate the potential Rh–duanphos-catalyzed asymmetric hydrogenation of β-secondary-amino ketones as a practical means for the enantioselective synthesis of γ-secondary-amino alcohols, two particularly interesting substrates, **9b** and **9h**, which are readily available from the corresponding ketones in one step, were explored with a low catalyst loading of the Rh complex **5a** (Scheme 3). When **9b**



Scheme 3. Enantioselective synthesis of pharmaceutical intermediates by a practical Rh-catalyzed asymmetric hydrogenation. S/C = substrate/catalyst ratio.

(1.42 g) was hydrogenated with of **5a** (1 mg) as the catalyst precursor (S/C = 6000) and K_2CO_3 (0.5 equiv) as the base in MeOH (10 mL) under H_2 (50 bar) at 50 °C for 12 h, γ-amino alcohol (*R*)-**10b** was isolated in 75% yield (TON > 4500) with 98% *ee*. When **9h** (1.52 g) was hydrogenated with **5a** (1 mg; S/C = 6000) under the same reaction conditions, (*S*)-**10h** was also isolated in 75% yield (TON > 4500) and >99% *ee*. Therefore, the described catalytic system is highly efficient for the reduction of β-secondary-amino ketones in terms of both enantioselectivity and reactivity. According to literature procedures,[5a,9] (*S*)-**10b** and (*S*)-**10h** can be subsequently converted into (*S*)-**1a** and (*S*)-**1d** in one step, respectively. Thus, these results provide one of the shortest (three steps overall) and most highly enantioselective (>98% *ee* without further recrystallization) syntheses of fluoxetine and duloxetine.

In conclusion, a series of β-secondary-amino ketone hydrochlorides were hydrogenated with remarkably high enantioselectivity, for the first time, with a Rh complex containing a highly electron-donating P-chiral bisphospholane ligand, **4**. For two substrates of particular interest, **9b** and **9h**, high turnover numbers were also achieved. These results established one of the shortest and most potentially practical means for the synthesis of enantiopure *N*-monosubstituted γ-amino alcohols, which are important pharmaceutical intermediates.

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