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Ruthenium-Catalyzed Asymmetric Hydrogenation of β-Keto-enamines: An Efficient Approach to Chiral γ-Amino Alcohols

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Abstract: A highly efficient and enantioselective hydrogenation of unprotected β-ketoenamines catalyzed with ruthenium(II) dichloro{(*S*)-(−)-2,2′-bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl}[(2*S*)-(+)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine] {Ru[(*S*)-xylbinap][(*S*)-daipen]Cl_2} has been successfully developed. This methodology provides a straightforward access to free γ-secondary amino alcohols, which are key building blocks for a variety of pharmaceuticals and natural products, with high yields (>99%) and excellent enantioselectivities (up to 99% *ee*) in all cases.

Keywords: asymmetric catalysis; enamines; enantioselectivity; hydrogenation; ruthenium

Enantiomerically pure amino alcohols and their derivatives are of great importance in synthetic and pharmaceutical chemistry.[1] Especially, γ-secondary amino alcohols **2** have drawn extensive attention as they are key intermediates for the synthesis of an important family of norepinephrine reuptake inhibitors, **1a–d**.[2] Enantiomerically active compounds **1a–d** are widely used as antidepressants in clinic medicine. Thus, a catalytic access to enantiomerically enriched amino alcohols **2** is of great significance and necessity for the pharmaceutical industry. The early synthesis of **2** mainly relied on chiral epoxide compounds[3] or enzyme catalysis[4]. Along with the development of catalytic asymmetric hydrogenation, several enantioselective syntheses of **2**, as well as **1**, have been reported based on hydrogenation of β-keto esters[5] or β-tertiary amino ketones.[6] However, the hydrogenation products need further tedious and complex transformations to afford the desired product **2**. Shimizu reported an elegant and succinct method to prepare chiral alcohols with high enantioselectivity and chemoselectivity by Cu(I)-catalyzed asymmetric hydrogenation of several heteroaromatic ketones and enones.[7] It is highly desired to develop an economic and efficient protocol for the synthesis of **2** based on direct asymmetric hydrogenation. Our group has already reported a direct hydrogenation of protected β-secondary amino ketones to prepare **2** with [Rh(DuanPhos)(NBD)]SbF_6 as catalyst, obtaining very high enantioselectivities (*ee* values up to 99%).[8] Another efficient method based on asymmetric hydrogenation of β-arylketoenamines was initially raised by a patent from Sumitomo Seika Chemicals Co.,[9] but the following detailed investigation was never reported. Herein, we present a Ru-catalyzed asymmetric hydrogenation of β-ketoenamines with *ee* values of >99% and turnover numbers (TON) = 1000 under mild reaction condition, which provides an alternative and efficient approach to chiral γ-amino alcohols **2** and the related pharmaceuticals.

The β-ketoenamine derivatives were synthesized directly from readily available methyl aryl ketones **4** through crossed Claisen condensation with ethyl formate, followed by amination with methylamine hydrochloride in a one-pot reaction (Scheme 1 and Table 1).[10] With our optimized procedure, substrates **3a–3j** were prepared in moderate yields as stable crystalline solids. Due to the intramolecular hydrogen bonding, only the *Z* configuration of the products was observed in most cases. It is worthy to note that the reaction afforded *Z*/*E* mixture products, **3b** and **3f**

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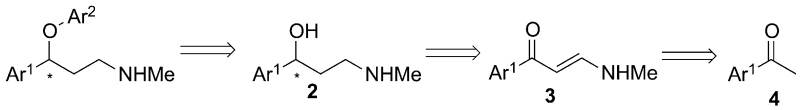
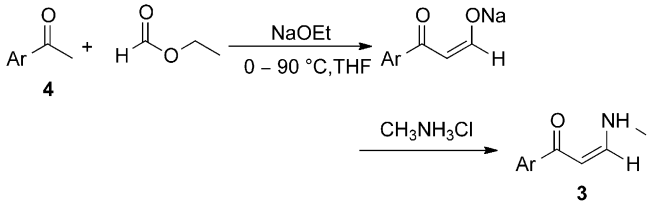


1a: Ar^1 = phenyl, Ar^2 = *p*-$CF_3C_6H_4$ (Fluoxetine)
1b: Ar^1 = phenyl, Ar^2 = *o*-MeC_6H_4 (Atomoxetine)
1c: Ar^1 = phenyl, Ar^2 = *o*-$MeOC_6H_4$ (Nisoxetine)
1d: Ar^1 = thiophenyl, Ar^2 = 1-naphthyl (Duloxetine)

Scheme 1. A retrosynthesis of the family of Fluoxetine by asymmetric hydrogenation.

Table 1. Synthesis of β-ketoenamine **3**.[a]



Entry	Ar	Ketoenamine	Isomer[b]	Yield [%][c]
1	C_6H_4	**3a**	*Z*	52
2	C_6H_4	**3b**	*Z*/*E* = 1/5	34
3	*p*-Me-C_6H_4	**3c**	*Z*	35
4	*p*-MeO-C_6H_4	**3d**	*Z*	66
5	*p*-F-C_6H_4	**3e**	*Z*	46
6	*p*-F-C_6H_4	**3f**	*Z*/*E* = 3/2	23
7	*p*-Cl-C_6H_4	**3g**	*Z*	44
8	*p*-Br-C_6H_4	**3h**	*Z*	56
9	2-thienyl	**3i**	*Z*	25
10	2-naphthyl	**3j**	*Z*	39

[a] All reactions were carried out in a one-pot reaction without separation of the intermediates, sodium enolates (see Supporting Information for the detailed procedure).
[b] *Z*/*E* ratios were determined by ^{1}H NMR spectroscopy.
[c] Yield of the isolated product.

(Table 1, entries 2 and 6), at lower reaction temperatures.

Inspired by the success of [Rh(DuanPhos)(NBD)]SbF_6 catalyst in the asymmetric hydrogenation of protected β-secondary amino ketones, **3a** was initially examined as the standard substrate in a series of rhodium-catalyzed hydrogenation reactions. However, neither [Rh(DuanPhos)(COD)]BF_4 nor [Rh(TangPhos)(COD)]BF_4, as well as other Rh-diphosphine catalytic systems could efficiently afford the desired amino alcohol product.[11] We have to turn our eyes to Ru-phosphine catalysts which are one of the most successful catalytic systems for asymmetric hydrogenation of ketones.[12] Although Ru[(*S*)-C_3-TunePhos-(*p*-cymene)]Cl_2 and Ru[(*S*)-C_3-TunePhos$(DMF)_n$]Cl_2 cannot provide the target product, Ru[(*S*)-xylbinap][(*S*)-daipen]Cl_2,[13] **L**, gave the product **2a** with 19.3% *ee* and 30.8% yield in methanol under 20 bar of hydrogen with 10 equivalents of potassium *tert*-butoxide. Solvent screening (Table 2, entries 1–8) indicated that using 2-propanol as solvent (entry 6) could dramatically enhance the enantioselectivity (98.7% *ee*) and reactivity (>99%) of **2a**. With 2-propanol as the optimal solvent, the effect of the hydrogen pressure was then investigated. Lowering the pressure to 1 bar can slightly increase the enantioselectivity to 99.5% *ee* (Table 2, entries 6, 9–11). Potassium *tert*-butoxide was found to be the base of choice and another inorganic base, potassium carbonate, also provided comparable reactivity and enantioselectivity, while an organic base, triethylamine, cannot promote the reaction at all (Table 2, entries 6, 12 and 13). The reaction time was tested as well, and set it to 24 h.

Encouraged by the above promising results, we further explored the asymmetric hydrogenation of a series of β-ketoenamine substrates, **3b–j**, under the optimized conditions with Ru[(*S*)-xylbinap][(*S*)-daipen]Cl_2 as the catalyst precursor. As shown in Table 3, entries 1–10, all the hydrogenation reactions smoothly proceeded to completion and provided γ-amino alcohols **2** in high yields (>99%) with very high enantioselectivities (99.0–99.7% *ee*). No obvious difference was observed between the reactivities and enantioselectivities of pure (*Z*)-β-ketoenamines and their *Z*/*E* mixtures (Table 3, entries 1, 2, 5 and 6). The hydrogenation reactions also showed a high tolerance to the electronic properties of the *para*-substituent on the phenyl ring regarding to both reactivity and enantioselectivity (Table 3, entries 3–8). β-Ketoenamine **3i**, with a heteroaromatic ring function, was hydrogenated to **2i** with high yield (>99%) and *ee* value (99.3%) as well (Table 3, entry 9).

In conclusion, we have reported that a variety of enantiomerically active γ-secondary amino alcohols, which are important pharmaceutical intermediates, can be efficiently prepared by asymmetric hydrogenation of β-ketoenamines with Ru[(*S*)-xylbinap][(*S*)-daipen]Cl_2 as catalyst. The very high reactivity and enantioselectivity suggest that this protocol provides one of the shortest and most practical accesses to the antidepressant, Fluoxetine, and related drugs. Studies aimed at further expanding the substrate scope for the synthesis of various chiral amino alcohols are in progress.

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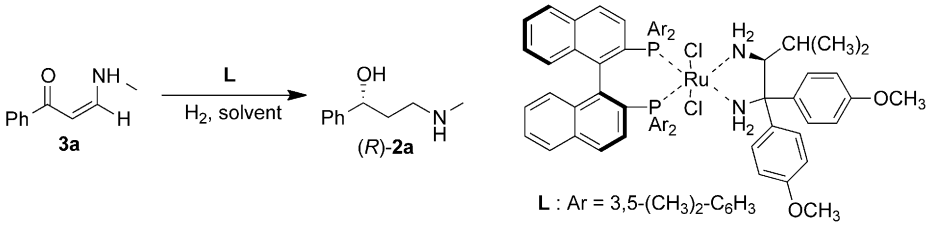
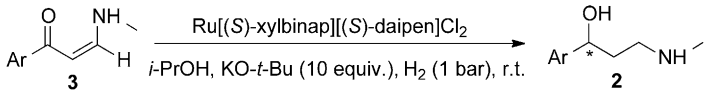
Table 2. Ru[(*S*)-xylbinap][(*S*)-daipen]Cl_2-catalyzed asymmetric hydrogenation of **3a** under various conditions.[a]



Entry	P_{H_2} [bar]	Solvent	Base	Yield [%][b]	*ee* [%][c]
1	20	MeOH	KO-*t*-Bu	31	19.3
2	20	CF_3CH_2OH	KO-*t*-Bu	N.R.	N.A.
3	20	toluene	KO-*t*-Bu	N.R.	N.A.
4	20	EtOAc	KO-*t*-Bu	N.R.	N.A.
5	20	CH_2Cl_2	KO-*t*-Bu	60	98.0
6	20	*i*-PrOH	KO-*t*-Bu	>99	98.7
7	20	1,4-dioxane	KO-*t*-Bu	53	99.3
8	20	THF	KO-*t*-Bu	49	98.1
9	1	*i*-PrOH	KO-*t*-Bu	>99	99.5
10	5	*i*-PrOH	KO-*t*-Bu	>99	99.4
11	10	*i*-PrOH	KO-*t*-Bu	>99	99.3
12	20	*i*-PrOH	K_2CO_3	92	98.1
13	20	*i*-PrOH	TEA	N.R.	N.A.

[a] The hydrogenation reactions were carried out under the described conditions for each entry with 1.0 mol% of **L** as the catalyst precursor (see Supporting Information for the general procedure).
[b] Yields were determined by ^{1}H NMR spectroscopy of the crude products.
[c] The *ee* values of **2a** were determined by chiral HPLC (with a Chiralpak OD-H column) analysis of its *N*-acyl derivative (see Supporting Information).

Table 3. Ru-catalyzed asymmetric hydrogenation of β-ketoenamines **3a–j**.[a]



Entry	Substrate	Ar	Isomer	Product	Yield [%][b]	*ee* [%] (Configuration)[c]
1	**3a**	C_6H_5	*Z*	**2a**	>99	99.5 (*R*)
2	**3b**	C_6H_5	*Z*/*E* = 1:5	**2b**	>99	99.0 (*R*)
3	**3c**	*p*-Me-C_6H_4	*Z*	**2c**	>99	99.4 (*R*)
4	**3d**	*p*-MeO-C_6H_4	*Z*	**2d**	>99	99.5 (*R*)
5	**3e**	*p*-F-C_6H_4	*Z*	**2e**	>99	99.6 (*R*)
6	**3f**	*p*-F-C_6H_4	*Z*/*E* = 3:2	**2f**	>99	99.7 (*R*)
7	**3g**	*p*-Cl-C_6H_4	*Z*	**2g**	>99	99.4 (*R*)
8	**3h**	*p*-Br-C_6H_4	*Z*	**2h**	>99	99.3 (*R*)
9	**3i**	2-thienyl	*Z*	**2i**	>99	99.3 (*R*)
10	**3j**	2-naphthyl	*Z*	**2j**	>99	99.5 (*R*)
11[e]	**3k**	C_6H_5	*Z*/*E* = 1:5	**2b**	>99	99.1(*R*)

[a] The hydrogenations were carried out in 2-propanol with 1.0 mol% of Ru[(*S*)-xylbinap] [(*S*)-daipen]Cl_2, 10 equivalents of KO-*t*-Bu under 1 bar H_2 at room temperature for 24 h (see Supporting Information for the general procedure).
[b] Yields were determined by ^{1}H NMR spectroscopy of the crude products.
[c] The *ee* values of **2a–2j** were determined by chiral HPLC (with a Chiralpak OD-H column) analysis of their *N*-acyl derivatives **5** (see Supporting Information). The absolute configurations of **2a** and **2j** were determined by comparing the sign of the optical rotations with reported data, while the absolute configurations of other products were assumed to be the same as **2a** and **2j**.
[e] The hydrogenation was carried out in 2-propanol with 0.1 mol% of Ru[(*S*)-xylbinap] [(*S*)-daipen]Cl_2, 10 equivalents of KO-*t*-Bu under 100 bar H_2 at 60 °C for 48 h.

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Experimental Section

General Remarks

All reactions and manipulations were performed in a nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 Å (230–450 mesh). ^{13}C NMR and ^{1}H NMR spectral data were recorded on Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm. Enantiomeric excess values were determined by chiral HPLC on Agilent 1200 Series equipment.

Substrate Preparation

To a suspension of sodium ethoxide (100 mmol, 6.81 g) in anhydrous THF (100 mL) was added ethyl formate (75 mmol) dropwise at 0 °C, followed by the addition of methyl aryl ketones (50 mmol). The resulting mixture was refluxed overnight, cooled to 0 °C, treated with 38.5 wt% methylamine hydrochloride solution (50 mmol) slowly, warmed up to 30 °C for 3 h, cooled to room temperature, and quenched with 0.2 wt% NaOH solution (20 mL) followed by removal of the solvent under vacuum. The residue was extracted with ethyl acetate (3 × 100 mL), combined the organic layer, washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The mixture was subjected to column chromatography on silica gel using hexane and ethyl acetate as the eluent to afford the substrates as stable crystalline solids.

General Procedure for Asymmetric Hydrogenation

A stock solution was made by mixing solid *trans*-$RuCl_2${(*S*)-xylbinap}-{(*S*)-daipen} and anhydrous KO-*t*-Bu at a 1:10 molar ratio in 2-propanol at room temperature for 30 min in a nitrogen-filled glovebox. A specified 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 2-propanol (2.9 mL). All the vials were placed in a steel autoclave into which 1 bar of hydrogen gas was charged. After stirring at room temperature for 24 h, the hydrogen was carefully released and the solution was concentrated and subjected to a short column of silica gel to afford the desired products **2**. The enantiomeric excess of **2** was determined by chiral HPLC using an OD-H column after being converted to its respective *N*-acyl dertivative **5**.

Acknowledgements

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