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Hydrogenation

Rhodium-catalyzed Asymmetric Hydrogenation of α-Dehydroamino Ketones: A General Approach to Chiral α-amino Ketones

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Abstract: Rhodium/DuanPhos-catalyzed asymmetric hydrogenation of aliphatic α-dehydroamino ketones has been achieved and afforded chiral α-amino ketones in high yields and excellent enantioselectives (up to 99% *ee*), which could be reduced further to chiral β-amino alcohols by LiAlH(*t*BuO)$_3$ with good yields. This protocol provides a readily accessible route for the synthesis of chiral α-amino ketones and chiral β-amino alcohols.

Chiral α-amino ketones as a versatile building block widely exist in natural products, drugs, and synthetic biologically active molecules.[1] Enantiopure β-amino alcohols can be obtained from chiral α-amino ketones, and this provides a direct route to the preparation of natural and pharmacologically active products (Figure 1).[2–4] For example, posaconazole is a triazole antifungal drug that is used to treat invasive infections by *Candida* species and *Aspergillus* species in severely immunocompromised patients. Considerable efforts have been devoted to developing new methodologies for the synthesis α-amino ketones. Typical methods include the reaction of organometallic reagents with α-amino acids and α-amino acids derivatives,[5] aza-benzoin reaction,[6] Friedel–Crafts-type reaction,[7] cross-coupling reaction[5e] as well as Dakin–West reaction[8]. However, most of these approaches suffer from drawbacks such as high catalyst loading and limited substrate scope. In addition, methods relating to the asymmetric synthesis of chiral aliphatic α-amino ketones remain underexploited. Therefore, it is highly desirable to develop new methods for the synthesis of chiral aliphatic α-amino ketones.

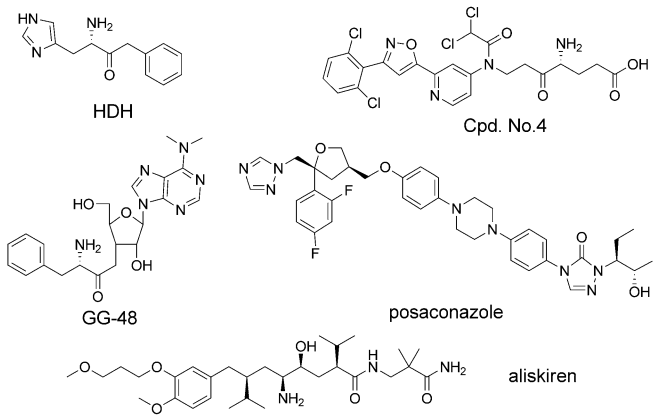

Figure 1. Representative drugs containing α-amino ketones and β-amino alcohols.

In the past decades, asymmetric hydrogenation[9] has become one of the most powerful strategies to obtain chiral compounds, especially for the synthesis of chiral amines and chiral alcohols.[10] In this context, our group has developed some efficient chiral diphosphine ligands which have been successfully used in the asymmetric hydrogenation of enamides, and developed a series of highly efficient methods for the asymmetric synthesis of chiral amines and their analogues.[11] However, asymmetric hydrogenation is rarely used in the highly enantioselective synthesis of chiral aliphatic α-amino ketones despite obvious advantages in the synthesis of chiral amines. The possible reason lies in that it is difficult to control the regioselectivities of hydrogenation of α-dehydroamino ketones. In addition, the enantioselectivities of asymmetric hydrogenation of aliphatic enamides is poor. Regioselective hydrogenation of α-dehydroamino ketones with high enantioselectivities remains a significant challenge. Herein, we report the asymmetric hydrogenation of aliphatic α-dehydroamino ketones to give α-amino ketones in high enantioselectivities and their applications in the synthesis of chiral β-amino alcohols (Scheme 1).

We began our experiments with 2-(benzylamino)pent-1-en-3-one (**2c**) as a model substrate, and various chiral diphosphine ligands were evaluated. As shown in Table 1, (*S*)-Binap exhibited good activity for this reaction but poor enantioselectivites (Table 1, entry 1). On the contrary, when Quinoxp was used as a ligand, it gave the desired product with poor yield but excellent enantioselectivity. When Tangphos, Josiphos, and C_3-Tunephos were employed (Figure 2), the results were improved dramatically, but it remained difficult to obtain high yields and high enantioselectivites simultaneously (Table 1, entries 2, 5, 6). To our delight, when (*S*,*S*′,*R*,*R*′)-DuanPhos developed in our lab was employed, it afforded the aliphatic α-

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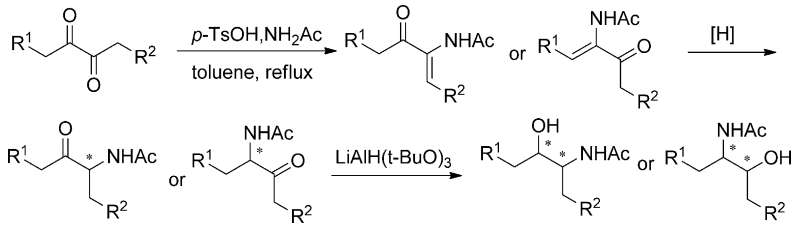
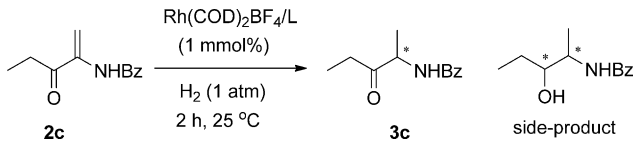


Scheme 1. Design and synthesis of α-amino ketones and β-amino alcohols.

Table 1. Ligand screening for Rh-catalyzed asymmetric hydrogenation.[a]



Entry	Ligand	Conversion[b] [%]	*ee*[c] [%]
1	(*S*)-Binap	98	9
2	(*R,S*)-JosiPhos	94	88
3	(*R,R*)-Quinoxp	23	93
4	(*S*)-SegPhos	–	–
5	(*S*)-C3-TunePhos	77	98
6	(*S,S,R,R*)-TangPhos	91	63
7	(*S,S,R,R*)-DuanPhos	>99	>99
8[e]	(*S,S,R,R*)-DuanPhos	>99	>99
9[f]	(*S,S,R,R*)-DuanPhos	>99	93

[a] All reactions were carried out with a substrate/Rh-L catalyst ratio of 100:1 in 1 mL THF at room temperature under 1 atm H_2 for 0.5 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a chiral phase. [d] Determined by ^{1}H NMR spectroscopy, the data in parenthesis is the ratio of **3c** and byproduct. [e] 0.5 h. [f] Substrate (1 mmol), cat. (0.1 mol%), THF (1 mL) at room temperature under 20 atm H_2 for 24 h.

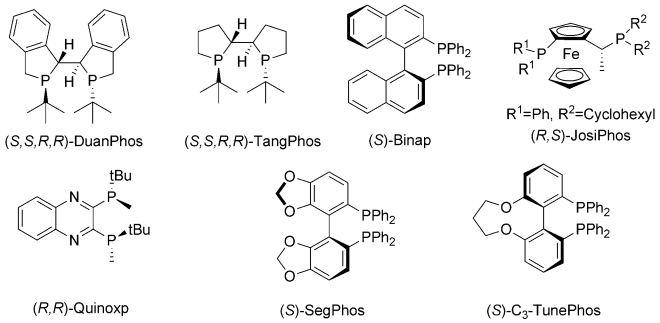
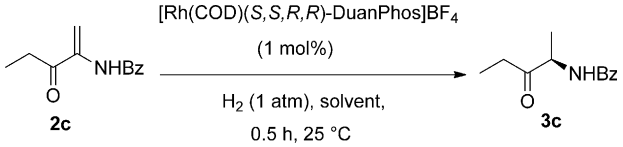


Figure 2. Structures of the phosphine ligands for hydrogenation of **2**.

amino ketone with 99.8% *ee*, although a large amount of by-product (amino alcohol) was obtained (Table 1, entry 7). Shortening of the reaction time to 0.5 h, **2c** was completely transformed to the α-amino ketone with high yield and excellent enantioselectivity (Table 1, entry 8). When we reduced the catalyst loading to 0.1 mol%, the reaction still proceeded smoothly but with a slightly loss in enantioselectivity (Table 1, entry 9). Solvent screening revealed that excellent enantioselectivities could be observed in all solvents examined, but that the solvent had a large influence on the conversion. Generally, excellent conversion was obtained when THF, dichloromethane, and alcohols were employed as solvents. At last, we chose THF as the optimal solvent as it gave desired products with slightly higher *ee* value (Table 2).

Under the optimized reaction conditions, a variety of aliphatic α-dehydroamino ketones were tested. As shown in Table 3, all substrates tested here could convert smoothly into the corresponding products with high yields and excellent *ee* values in a short time (**3a–3i**). Generally, di- and trisubstituted α-dehydroamino ketones could be used

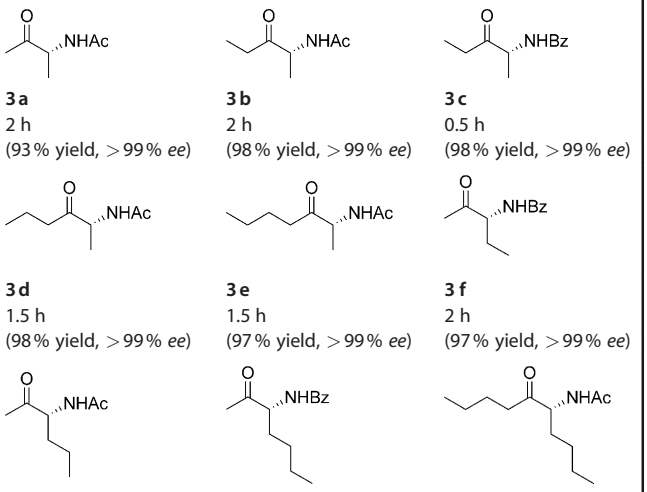
Table 2. Solvent screening for Rh-catalyzed asymmetric hydrogenation.[a]



Entry	Solvent	Conversion[b] [%]	*ee*[c] [%]
1	THF	>99	99.8
2	EtOH	>99	99.4
3	*i*PrOH	>99	99.5
4	MeOH	>99	98.2
5	CH_2Cl_2	>99	99.1
6	Toluene	85	99.7
7	Dioxane	5	96.9

[a] All reactions were carried out with a substrate/Rh-DuanPhos catalyst ratio of 100:1 in 1 mL solvent at room temperature under 1 atm H_2 for 0.5 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC or GC on a chiral phase.

Table 3. Asymmetric hydrogenation of α-dehydroamino ketone by Rh/(*S,S′,R,R′*)-DuanPhos.[a]



[a] Reaction conditions: **2** (0.1 mmol), Rh(cod)-DuanPhos (0.001 mmol), THF (1 mL), under 1 atm H_2 at room temperature. Yields of isolated products are given. The enantioselectivities were determined by HPLC or GC using a chiral stationary phase.

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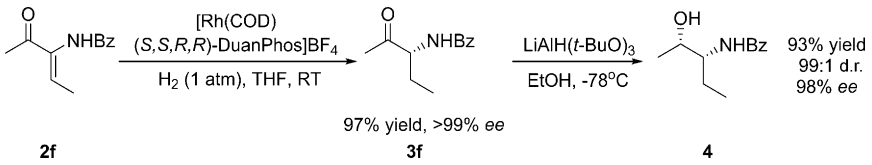
in this reaction, and they gave the corresponding α-amino ketones with satisfactory results. With regard to the R^1 and R^2 groups, the length of the alkyl chain had no obvious influence on the yields and *ee* values of the products. Besides, when we changed the N-protecting group of the substrates, no influence on the result was observed (**3 b**, **3 c**).



Scheme 2. Synthesis of *N*-((2*S*,3*R*)-2-hydroxypentan-3-yl)benzamide **4**.

To illustrate the potential usefulness of this approach, a concise synthetic route to chiral 3-aminopentan-2-ol, a key chiral intermediate in the synthesis of posaconzole, an important antibacterial drug, has been developed. Using LiAlH(*t*BuO)$_3$ as reducing regent, α-amino ketone **3 f** was readily converted into 3-aminopentan-2-ol in good yield and without loss in enantioselectivity (Scheme 2).[12,13]

In summary, we found Rh/DuanPhos to be an effective catalyst for the asymmetric hydrogenation of α-dehydroamino ketones, affording aliphatic α-amino ketones in high yields and excellent enantioselectivities. This method is applied under mild conditions and has a broad substrate scope, providing a very efficient and general route to the synthesis of chiral aliphatic α-amino ketones and α-amino alcohols. This protocol may find important applications for synthesizing chiral pharmaceutical products containing α-amino ketones and β-amino alcohols. Further studies on expanding the substrate scope and applications are undergoing in our lab.

Experimental Section

General hydrogenation procedure: In a nitrogen-filled glovebox, the Rh complex (0.001 mmol) was dissolved in anhydrous THF (0.1 mL), and the solution was equally divided into 10 vials charged with α-dehydroamino ketones (0.1 mmol) in anhydrous THF solution (1.0 mL). The resulting vials were transferred to an autoclave, which was charged with 1 atm of H_2, and the reaction mixtures were stirred at room temperature for a specified time. The hydrogen gas was then released slowly, and the solution was concentrated and passed through a short column of silica gel to remove the metal complex. The chiral α-amino ketones were then analyzed by HPLC or GC on a chiral stationary phase to determine the enantiomeric excesses.

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Keywords: asymmetric catalysis · hydrogenation · P ligands · rhodium · α-amino ketones

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[13] The product's absolute configuration was confirmed as (*R*) by comparing the specific rotation and the NMR spectrum of **4** with data reported in the literature (see ref. 12b).

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