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## Enantio- and diastereoselective synthesis of $\gamma$ -amino alcohols†

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**The  $\gamma$ -amino alcohol structural motif is often encountered in drugs and natural products. We developed two complementary catalytic diastereoselective methods for the synthesis of *N*-PMP-protected  $\gamma$ -amino alcohols from the corresponding ketones. The *anti*-products were obtained through Ir-catalyzed asymmetric transfer hydrogenation, the *syn*-products via Rh-catalyzed asymmetric hydrogenation.**

The growing number of enantio- and diastereomerically pure drug candidates has driven the advancement of stereoselective synthetic strategies.<sup>1,2</sup> The  $\gamma$ -amino alcohol moiety is often encountered in biologically relevant molecules and hence, general procedures are desired to selectively prepare all of its possible diastereoisomers. Examples of molecules containing the  $\gamma$ -amino alcohol structural motif include the drugs Ritonavir and Lopinavir (both anti-HIV)<sup>3</sup> and several 4-hydroxyleucine derivatives (anti-obesity) (Fig. 1).<sup>4</sup>

Despite the abundance of the  $\gamma$ -amino alcohol structure in synthetically relevant targets, relatively few generally applicable stereoselective methods are available for the construction of such a moiety. Undoubtedly the most straightforward route involves diastereoselective reduction of a  $\beta$ -amino ketone Mannich product by employing a suitable hydride donor. Besides several methods for the reduction of  $\alpha$ -chiral  $\beta$ -amino ketones,<sup>5–7</sup> a number of reports on the stoichiometric reduction of  $\beta$ -branched  $\beta$ -amino ketones (with a methylene adjacent to the amine function) have been disclosed.<sup>8–11</sup> These include the diastereoselective

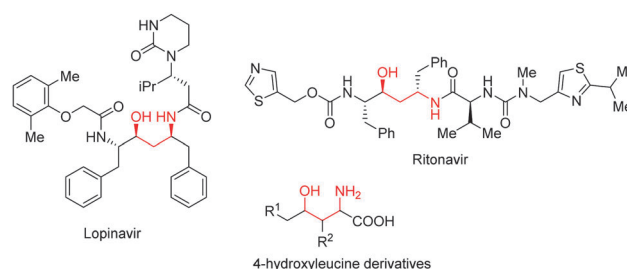


Fig. 1 Pharmaceutically relevant  $\gamma$ -amino alcohols.

reduction of *N*-sulfonyl-protected  $\gamma$ -hydroxyimines,<sup>12</sup> *syn*-selective reductive amination of  $\beta$ -hydroxy ketones with *p*-anisidine and polymethylhydrosiloxane,<sup>13</sup> and dynamic kinetic resolution of *N*-Boc-protected  $\gamma$ -amino ketones.<sup>14</sup> As an alternative, amino alcohols can be prepared through transition metal-catalyzed hydrogenation of  $\beta$ -amino ketones,<sup>15</sup> although these methodologies have more generally been reported for the hydrogenation of substances without  $\beta$ -chirality.<sup>16</sup>

We envisaged that robust enantioselective access to  $\gamma$ -amino alcohols may proceed *via* a proline-catalyzed Mannich reaction to yield *N*-PMP-protected amino ketones, diastereoselective reduction of the keto function, and subsequent removal of the PMP protecting group.<sup>17</sup> In this report, we describe that *N*-PMP-protected  $\beta$ -amino ketones can be efficiently converted into each of the corresponding *syn*- and *anti*- $\gamma$ -amino alcohols in a highly diastereoselective manner. Both hydrogenation and transfer hydrogenation have found many applications in stereoselective reduction of alkynes, alkenes, imines and ketones.<sup>18</sup> Surprisingly, no literature precedence on the diastereoselective (transfer) hydrogenation of chiral  $\beta$ -amino ketones existed at the start of our research, while on the other hand  $\beta$ -hydroxy ketones have shown to be suitable hydrogenation substrates.<sup>19,20</sup> In transfer hydrogenations, 2-propanol or a formic acid/triethylamine mixture is used as the source of hydrogen, which is reversibly transferred to the substrate molecule. Due to this reversibility, a careful analysis of the reaction progress and selectivity is required. We started our investigations on asymmetric

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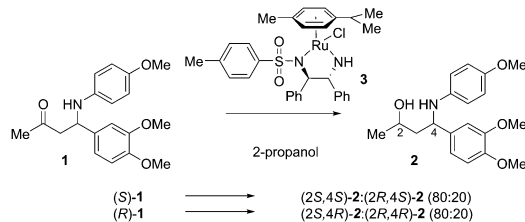
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Scheme 1 Ru/(*R,R*)-TsDPEN-catalyzed ATH of ketone **1**.

transfer hydrogenation (ATH) of *N*-PMP-protected  $\beta$ -amino ketone **1**.

Using the well-established Ru/TsDPEN complex **3** as the catalyst, we observed a clean conversion into the desired  $\gamma$ -amino alcohols with a moderate dr (80:20), which irrespective of the existing chiral center depended on the catalyst chirality (Scheme 1). Encouraged by these initial results we also explored the use of iridium-based ATH catalysts. We prepared catalysts **4** by heating a solution of a suitable iridium precursor (*i.e.* [IrCp\*Cl<sub>2</sub>]<sub>2</sub>) and an amino acid amide in the presence of an inorganic base (*e.g.* K<sub>2</sub>CO<sub>3</sub>) according to a modified protocol disclosed by Verzijl.<sup>21</sup> The inorganic base was removed by filtration to suppress possible elimination of *p*-anisidine prior to reduction. Preferably,  $\alpha,\alpha$ -disubstituted amino acids were employed to avoid the risk of catalyst racemization.

To our satisfaction, exposure of benchmark substrate **1** to these catalysts resulted in high diastereoselectivities. When *D*- $\alpha$ -Me-phenylglycine amide was used as the ligand, conversion of (*S*)-**1** into the corresponding *anti*-amino alcohol **2** proceeded in a diastereomeric ratio of 96:4 (Table 1, entry 1), while the (*R*)-aminoketone led to a 1:1 formation of amino alcohols (entry 2). This implies that during iridium-catalyzed reduction, the existing chiral center has a large impact on the stereochemical outcome of the transfer hydrogenation. The influence of the preexisting chirality in terms of a match and mismatch with the ligand was confirmed by employing achiral Aib-NH<sub>2</sub> as the ligand (entry 3). In the presence of this achiral catalyst, a diastereomeric ratio of 84:16 was observed for the products. Replacing substituent R<sup>2</sup> of catalyst **4a** with a Bn group (*i.e.* **4d**)

Table 1 Screening of Ir-based amino acid amide catalysts **4a–e** for ATH of aminoketone **1**<sup>a</sup>

Entry	sm	R <sup>1</sup>	R <sup>2</sup>	Cat	Ratio ( <b>2</b> )
1	( <i>S</i> )- <b>1</b>	Me	Ph	<b>4a</b>	96:4 <sup>b</sup>
2	( <i>R</i> )- <b>1</b>	Me	Ph	<b>4a</b>	50:50 <sup>c</sup>
3	( <i>S</i> )- <b>1</b>	Me	Me	<b>4b</b>	84:16 <sup>b</sup>
4	( <i>S</i> )- <b>1</b>	Me	Bn	<b>4d</b>	63:37 <sup>b</sup>
5	( <i>R</i> )- <b>1</b>	Me	Bn	<b>4d</b>	2:98 <sup>c</sup>
6	( <i>R</i> )- <b>1</b>	Bn	Ph	<b>4c</b>	0:100 <sup>c</sup>
7	( <i>S</i> )- <b>1</b>	Bn	Ph	<b>4c</b>	47:53 <sup>b</sup>

<sup>a</sup> Reaction conditions: 4–6 mol% catalyst, rt 25 min–25 h. <sup>b</sup> (2*R*,4*S*)/(2*S*,4*S*). <sup>c</sup> (2*R*,4*R*)/(2*S*,4*R*).

Table 2 Preparative ATH of  $\beta$ -amino ketones<sup>a</sup>

Entry	sm	R <sup>1</sup>	pr	dr <sup>b</sup>	Yield <sup>c</sup>
1	( <i>S</i> )- <b>1</b>	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>2</b>	96:4	100
2	( <i>S</i> )- <b>6</b>	4-FC <sub>5</sub> H <sub>4</sub>	<b>10</b>	95:5	88
3	( <i>S</i> )- <b>7</b>	2-MeC <sub>6</sub> H <sub>4</sub>	<b>11</b>	97:3	76
4	( <i>R</i> )- <b>8</b>	iBu	<b>12</b>	76:24 <sup>d</sup>	99
5	( <i>S</i> )- <b>9</b>	CO <sub>2</sub> Et	<b>13</b>	79:21	100

<sup>a</sup> Reaction conditions: ketone (1.0 equiv.), (IrCp\*Cl<sub>2</sub>)<sub>2</sub> (0.02 equiv.),  $\alpha$ -Me-phenylglycine-NH<sub>2</sub> (0.20 equiv.), K<sub>2</sub>CO<sub>3</sub> (3 equiv.), 2-propanol, rt, 1.5–20 h. <sup>b</sup> (2*R*,4*S*):(2*S*,4*S*) (determined by HPLC). <sup>c</sup> Isolated yield. <sup>d</sup> Absolute configuration = (2*R*,4*R*):(2*S*,4*R*).

resulted in decreased selectivity (entry 4), whereas nearly complete selectivity was obtained with the same catalyst **4d** for the (*R*)-substrate (entry 5). The combination of phenyl and benzyl substituents showed again a clear match (entry 6, diastereoselectivity of 0:100) and mismatch (entry 7).

Although slightly better results were obtained with  $\alpha$ -benzylated phenylglycinamide as the ligand, we explored the substrate scope of the stereoselective ATH with the  $\alpha$ -methyl- $\alpha$ -phenyl substituted glycineamide-based catalyst (**4a**) because of its straightforward accessibility. The  $\beta$ -amino ketone substrates were prepared *via* the asymmetric proline-catalyzed Mannich reaction.<sup>22,23</sup> The results in Table 2 led us to conclude that ATH of  $\beta$ -amino ketones is widely applicable. In all examples we observed a reasonable to good diastereoselectivity, with the best selectivities obtained for R<sup>1</sup> = Ar. In addition, it is worth mentioning that we have previously successfully deprotected both diastereoisomers of PMP-protected amino alcohol **2** using oxidative enzymatic conditions.<sup>17b</sup>

With an efficient method for the *anti*-selective preparation of  $\gamma$ -amino alcohols in hand, we realized that extensive screening of other metal/ligand combinations could possibly deliver

Table 3 Preparative AH of  $\beta$ -amino ketones<sup>a</sup>

Entry	sm	R <sup>1</sup>	<i>t</i> (h)	pr	dr <sup>b</sup>	Yield <sup>c</sup>
1	( <i>S</i> )- <b>1</b>	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	19 <sup>d</sup>	<b>2</b>	> 95:5	77
2	( <i>S</i> )- <b>6</b>	4-FC <sub>5</sub> H <sub>4</sub>	44 <sup>e</sup>	<b>10</b>	> 95:5	76
3	( <i>S</i> )- <b>7</b>	2-MeC <sub>6</sub> H <sub>4</sub>	44 <sup>e</sup>	<b>11</b>	> 95:5	81
4	( <i>R</i> )- <b>8</b>	iBu	15 <sup>d</sup>	<b>12</b>	> 95:5 <sup>f</sup>	77
5	( <i>S</i> )- <b>9</b>	CO <sub>2</sub> Et	17 <sup>d</sup>	<b>13</b>	> 95:5	56

<sup>a</sup> Reaction conditions: substrate (1.0 equiv.), Rh(COD)<sub>2</sub>BF<sub>4</sub> (0.05 equiv.), (*R*)-BINAP (0.05 equiv.), r.t., 15–44 h or substrate (1.0 equiv.), Rh(COD)<sub>2</sub>BF<sub>4</sub> (0.30 equiv.), (*R*)-BINAP (0.030 equiv.), 50 °C, 15–44 h. <sup>b</sup> (2*S*,4*S*):(2*R*,4*S*) (determined by HPLC). <sup>c</sup> Isolated yields. <sup>d</sup> 50 °C. <sup>e</sup> rt. <sup>f</sup> (2*S*,4*R*):(2*R*,4*R*) (determined by HPLC).



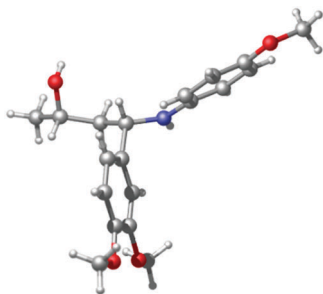


Fig. 2 Crystal structure representation of (2S,4S)-2 (ORTEP probability level 50%).<sup>24</sup>

$\gamma$ -amino alcohols with *syn*-selectivity. We nevertheless resorted to hydrogenation with molecular hydrogen for the synthesis of the *syn*-congeners. We discovered that hydrogenation of  $\beta$ -amino ketones in the presence of a catalyst *in situ* prepared from Rh(COD)<sub>2</sub>BF<sub>4</sub> and a C<sub>2</sub>-symmetric ligand such as (*R*)-BINAP (5) (Table 3), produced the desired *syn*- $\gamma$ -amino alcohols with excellent diastereoselectivity.

Again we observed a strong effect of the existing chiral center on the diastereoselectivity. Upon hydrogenation of (*S*)-1 with Rh/(*R*)-BINAP, pure (2S,4S)-2 was obtained, whereas with Rh/(*S*)-BINAP the ratio (*R,S*) vs. (*S,S*) was 70:30. Dichloromethane appeared to be the most suitable solvent with respect to solubility of the starting material, diastereoselectivity and reaction rate. To investigate the scope and limitations, we subsequently hydrogenated a number of aromatic, aliphatic and carboxylic  $\beta$ -aminoketones on preparative scale (Table 3).

In some cases, the reactions proceeded somewhat slowly, despite the use of higher catalyst loadings (entries 2 and 3). In all cases, however, nearly exclusive formation of the desired *syn*-diastereoisomer was observed in combination with good yields.

Finally, to verify the assigned stereochemical outcome, we prepared (2S,4S)-2 on a larger scale, after which X-ray crystallographic analysis of the product proved that Rh/(*R*)-BINAP (5) hydrogenation of (*S*)-1 indeed led to formation of the *syn*-product ((2S,4S)-2, Fig. 2).

We have developed two complementary methods for the hydrogenation of  $\beta$ -amino ketones to the corresponding  $\gamma$ -amino alcohols. The *anti*-products can be obtained through ATH, in which 2-propanol is employed as the hydrogen donor and an Ir/ $\alpha$ -substituted-amino acid amide complex as the catalyst. *syn*-Products are accessible by asymmetric hydrogenation under hydrogen pressure in the presence of a Rh-based BINAP catalyst. In combination with the proline-catalyzed Mannich reaction, these methods provide powerful tools for the enantio- and diastereoselective synthesis of all four diastereomers of  $\gamma$ -amino alcohols.

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- 23 It should be noted that in some instances, Mannich ketones were prone to partial racemization over time. We hypothesize that racemization occurs *via* catalysis by trace impurities in the Mannich product samples, because ketones 6–9 were oils and purified by troublesome column chromatography, while 1 was purified through crystallization and the resulting crystals appeared more stable.
- 24 xyz file generated with Mercury 3.5.1 (<http://www.ccdc.cam.ac.uk/Solutions/CSDSystem/Pages/Mercury.aspx>). Picture generated with CYLview, 1.0b; C. Y. Legault, Université de Sherbrooke, 2009 (<http://www.cylview.org>). CCDC 1400959.

