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Enantio- and Diastereoselective Synthesis of γ -Amino Alcohols

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Abstract The γ -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 γ -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.^{1,2} The γ -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 γ -amino alcohol structural motif include the drugs Ritonavir and Lopinavir (both anti-HIV)³ and several 4-hydroxyleucine derivatives (anti-obesity).⁴

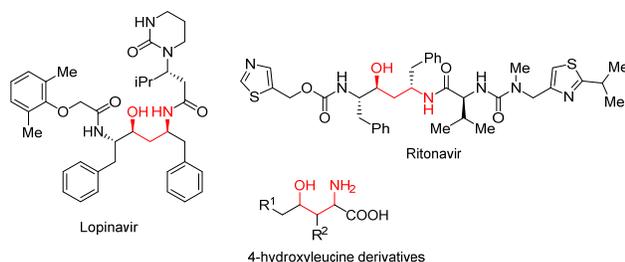


Figure 1. Pharmaceutically relevant γ -amino alcohols

Despite the abundance of the γ -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 β -amino ketone Mannich product by employing a suitable hydride donor. Besides several methods for the reduction of α -chiral β -amino ketones,^{5–7} a number of reports on the stoichiometric reduction of β -branched β -amino ketones (with a methylene adjacent to the amine function) have been disclosed.^{8–11} These include the diastereoselective reduction of *N*-sulfonyl-protected γ -hydroxyimines,¹² *syn*-selective reductive amination of β -hydroxy ketones with *p*-anisidine and polymethylhydrosiloxane,¹³ and dynamic kinetic resolution of *N*-Boc-protected γ -amino ketones.¹⁴ As an alternative, amino alcohols can be prepared through transition metal-catalyzed hydrogenation of β -amino ketones,¹⁵ although these methodologies have more generally been reported for the hydrogenation of substances without β -chirality.¹⁶

We envisaged that robust enantioselective access to γ -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.¹⁷ In this report, we describe that *N*-PMP-protected β -amino ketones can be efficiently converted into each of the corresponding *syn*- and *anti*- γ -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.¹⁸ Surprisingly, no literature precedence on the diastereoselective (transfer) hydrogenation of chiral β -amino ketones existed at the start of our research, while on the other hand β -hydroxy ketones have shown to be suitable hydrogenation substrates.^{19,20} 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 transfer hydrogenation (ATH) of *N*-PMP-protected β -amino ketone **1**.

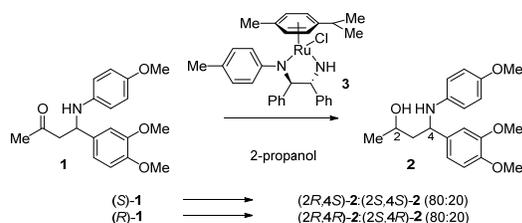
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Scheme 1. Ru/(*R,R*)-TsDPEN-catalyzed ATH of ketone **1**

Using the well-established Ru/TsDPEN complex **3** as the catalyst, we observed a clean conversion into the desired γ -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*Cl₂]₂) and an amino acid amide in the presence of an inorganic base (*e.g.* K₂CO₃) according to a modified protocol disclosed by Verzijl.²¹ The inorganic base was removed by filtration to suppress possible elimination of *p*-anisidine prior to reduction. Preferably, α,α -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- α -Methylglycine 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-NH₂ 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 R² of catalyst **4a** with a Bn group (*i.e.* **4d**) 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, diastereoselectivity of 0:100) and mismatch (entry 7).

Table 1. Screening of Ir-based amino acid amide catalysts **4a-e** for ATH of aminoketone **1**^a

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

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

Although slightly better results were obtained with α -benzylated phenylglycinamide as the ligand, we explored the substrate scope of the stereoselective ATH with the α -methyl- α -phenyl substituted glycinamide-based catalyst (**4a**) because of its straightforward accessibility. The β -amino ketone substrates were prepared via the asymmetric proline-catalyzed Mannich reaction.^{22,23} The results in Table 2 led us to conclude that ATH of β -amino ketones is widely applicable. In all examples we observed a reasonable to good diastereoselectivity, with the best selectivities obtained for R¹ = 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.^{17b} With an efficient method for the *anti*-selective preparation of γ -amino alcohols in hand, we realized that extensive screening of other metal/ligand combinations could possibly deliver γ -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 β -amino ketones in the presence of a catalyst in situ prepared from Rh(COD)₂BF₄ and a C₂-symmetric ligand such as (*R*)-BINAP (**5**) (Table 3), produced the desired *syn*- γ -amino alcohols with excellent diastereoselectivity.

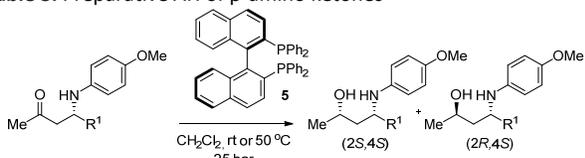
Table 2. Preparative ATH of β -amino ketones^a

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

^a Reaction conditions: ketone (1.0 equiv), [IrCp*Cl₂]₂ (0.02 equiv), α -Me-phenylglycine-NH₂ (0.20 equiv), K₂CO₃ (3 equiv), 2-propanol, rt, 1.5–20 h. ^b(2*R*,4*S*):(2*S*,4*S*) (determined by HPLC). ^c isolated yield. ^dabsolute configuration = (2*R*,4*R*):(2*S*,4*R*).

Again we observed a strong effect of the existing chiral center on the diastereoselectivity. Upon hydrogenation of (*S*)-**1** with Rh/(*R*)-BINAP, pure (2*S*,4*S*)-**2** was obtained, whereas with Rh/(*S*)-BINAP the ratio (*R,S*) vs (*S,S*) was 70:30 (both not shown). 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 β -aminoketones on preparative scale (Table 3).

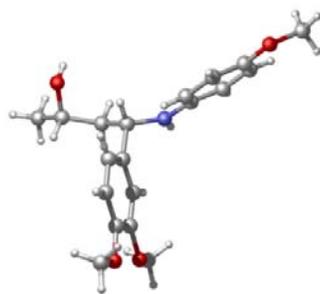
In some cases, the reactions proceeded somewhat slowly, despite the use of higher catalyst loadings (entries 2 and 3). In all cases, however, nearly exclusive formation of the desired *syn*-diastereoisomer was observed in combination with good yields. Finally, to verify the assigned stereochemical outcome, we prepared (2*S*,4*S*)-**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 ((2*S*,4*S*)-**2**, Figure 2).

Table 3. Preparative AH of β -amino ketones^a


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

^aReaction conditions: substrate (1.0 equiv), Rh(COD)₂BF₄ (0.05^e or 0.30^d equiv), (R)-BINAP (0.05^e or 0.30^d equiv), 15–44 h. ^b(2S,4S):(2R,4S) (determined by HPLC). ^cisolated yields. ^d50°C. ^ert. ^f(2S,4R):(2R,4R) (determined by HPLC).

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**, Figure 2).

**Figure 2.** Crystal structure representation of (2S,4S)-**2** (ORTEP probability level 50%)²⁴

Conclusions

We have developed two complementary methods for the hydrogenation of β -amino ketones to the corresponding γ -amino alcohols. The *anti*-products can be obtained through ATH, in which 2-propanol is employed as the hydrogen donor and an Ir/ α -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 γ -amino alcohols.

Acknowledgements

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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>). Crystal structure data can be obtained free of charge via the Internet at <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (deposition no. CCDC 1400959).