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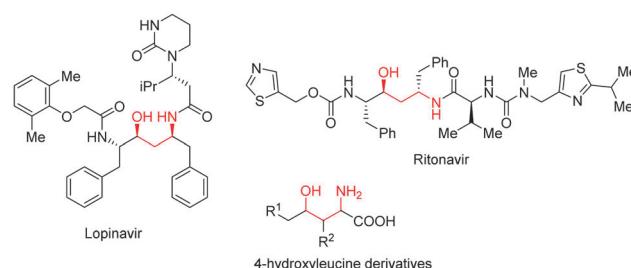
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The γ -amino alcohol structural motif is often encountered in drugs and natural products. We developed two complementary catalytic diastereoselective methods for the synthesis of *N*-PMP-protected γ -amino alcohols from the corresponding ketones. The *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) (Fig. 1).⁴

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


 Fig. 1 Pharmaceutically relevant γ -amino alcohols.

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

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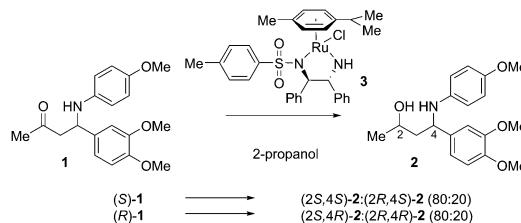
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† Electronic supplementary information (ESI) available: Experimental data, characterization data and crystal data and structure refinements. CCDC 1400959. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc04445f

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

transfer hydrogenation (ATH) of *N*-PMP-protected β -amino 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 α -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-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)

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 (2R,4S)/(2S,4S). ^c (2R,4R)/(2S,4R).

Table 2 Preparative ATH of β -amino ketones^a

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	iBu	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 (2R,4S):(2S,4S) (determined by HPLC). ^c Isolated yield.

^d Absolute configuration = (2R,4R):(2S,4R).

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 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

Table 3 Preparative AH of β -amino ketones^a

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

^a Reaction conditions: substrate (1.0 equiv.), Rh(COD)₂BF₄ (0.05 equiv.), (*R*)-BINAP (0.05 equiv.), r.t., 15–44 h or substrate (1.0 equiv.), Rh(COD)₂BF₄ (0.30 equiv.), (*R*)-BINAP (0.030 equiv.), 50 °C, 15–44 h.

^b (2S,4S):(2R,4S) (determined by HPLC). ^c Isolated yields. ^d 50 °C. ^e rt. ^f (2S,4R):(2R,4R) (determined by HPLC).



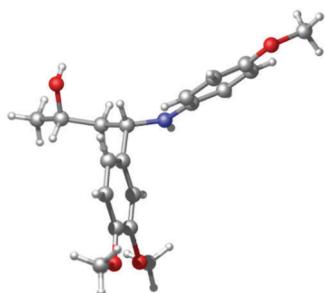


Fig. 2 Crystal structure representation of (2S,4S)-2 (ORTEP probability level 50%).²⁴

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 $\text{Rh}(\text{COD})_2\text{BF}_4$ and a C_2 -symmetric ligand such as (*R*)-BINAP (5) (Table 3), produced the desired *syn*- γ -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 $\text{Rh}/(\text{R})\text{-BINAP}$, pure (2*S*,4*S*)-2 was obtained, whereas with $\text{Rh}/(\text{S})\text{-BINAP}$ 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 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 $\text{Rh}/(\text{R})\text{-BINAP}$ (5) hydrogenation of (*S*)-1 indeed led to formation of the *syn*-product ((2*S*,4*S*)-2, Fig. 2).

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.

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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.

