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Enantio- and diastereoselective synthesis of γ-amino alcohols†

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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 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]

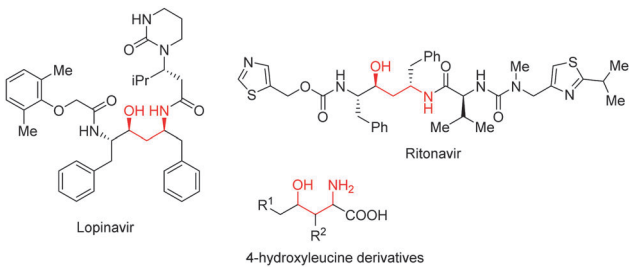

Fig. 1 Pharmaceutically relevant γ-amino alcohols.

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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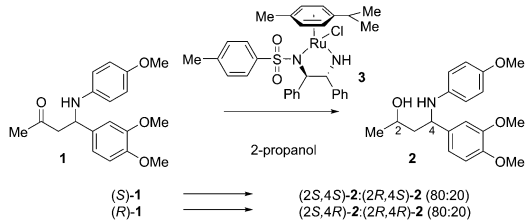


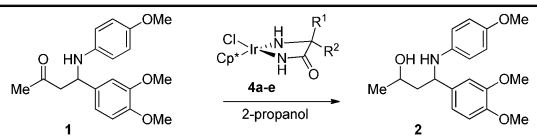
Scheme 1 Ru/(*R*,*R*)-TsDPEN-catalyzed ATH of ketone **1**.

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.* $[IrCp^*Cl_2]_2$) and an amino acid amide in the presence of an inorganic base (*e.g.* K_2CO_3) 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-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_2 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^2 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).

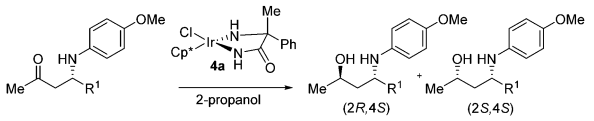
Table 1 Screening of Ir-based amino acid amide catalysts **4a–e** for ATH of aminoketone **1**[a]



Entry	sm	R^1	R^2	Cat	Ratio (**2**)
1	(*S*)-**1**	Me	Ph	**4a**	96 : 4[b]
2	(*R*)-**1**	Me	Ph	**4a**	50 : 50[c]
3	(*S*)-**1**	Me	Me	**4b**	84 : 16[b]
4	(*S*)-**1**	Me	Bn	**4d**	63 : 37[b]
5	(*R*)-**1**	Me	Bn	**4d**	2 : 98[c]
6	(*R*)-**1**	Bn	Ph	**4c**	0 : 100[c]
7	(*S*)-**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*).

Table 2 Preparative ATH of β-amino ketones[a]



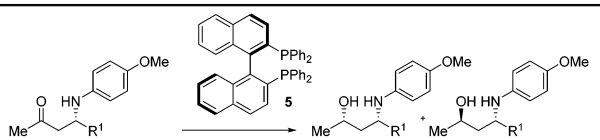
Entry	sm	R^1	pr	dr[b]	Yield[c]
1	(*S*)-**1**	3,4-$(MeO)_2C_6H_3$	**2**	96 : 4	100
2	(*S*)-**6**	4-FC_5H_4	**10**	95 : 5	88
3	(*S*)-**7**	2-MeC_6H_4	**11**	97 : 3	76
4	(*R*)-**8**	iBu	**12**	76 : 24[d]	99
5	(*S*)-**9**	CO_2Et	**13**	79 : 21	100

[a] Reaction conditions: ketone (1.0 equiv.), $(IrCp^*Cl_2)_2$ (0.02 equiv.), α-Me-phenylglycine-NH_2 (0.20 equiv.), K_2CO_3 (3 equiv.), 2-propanol, rt, 1.5–20 h. [b] (2*R*,4*S*) : (2*S*,4*S*) (determined by HPLC). [c] Isolated yield. [d] Absolute configuration = (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 R^1 = 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	(*S*)-**1**	3,4-$(MeO)_2C_6H_3$	19[d]	**2**	> 95 : 5	77
2	(*S*)-**6**	4-FC_5H_4	44[e]	**10**	> 95 : 5	76
3	(*S*)-**7**	2-MeC_6H_4	44[e]	**11**	> 95 : 5	81
4	(*R*)-**8**	iBu	15[d]	**12**	> 95 : 5[f]	77
5	(*S*)-**9**	CO_2Et	17[d]	**13**	> 95 : 5	56

[a] Reaction conditions: substrate (1.0 equiv.), $Rh(COD)_2BF_4$ (0.05 equiv.), (*R*)-BINAP (0.05 equiv.), r.t., 15–44 h or substrate (1.0 equiv.), $Rh(COD)_2BF_4$ (0.30 equiv.), (*R*)-BINAP (0.030 equiv.), 50 °C, 15–44 h. [b] (2*S*,4*S*) : (2*R*,4*S*) (determined by HPLC). [c] Isolated yields. [d] 50 °C. [e] rt. [f] (2*S*,4*R*) : (2*R*,4*R*) (determined by HPLC).

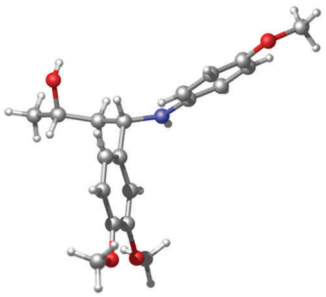


Fig. 2 Crystal structure representation of (2*S*,4*S*)-**2** (ORTEP probability level 50%).[24]

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 $Rh(COD)_2BF_4$ 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 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. 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**, 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.