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Highly Diastereoselective Heterogeneously Catalyzed Hydrogenation of Enamines for the Synthesis of Chiral β-Amino Acid Derivatives

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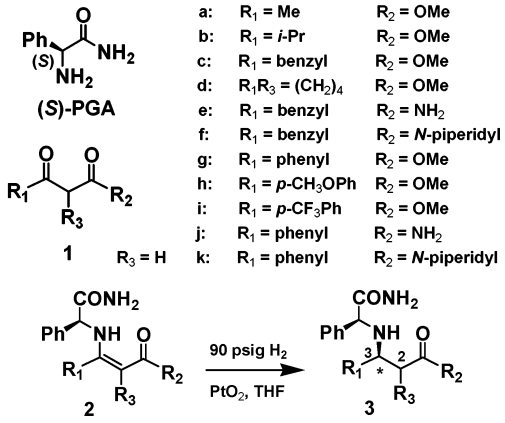
Enantiopure β-amino acids and their derivatives are components of a variety of important natural products and targets for pharmaceutical research.[1] A useful method for preparing compounds of this class in high enantioselectivity involves enantioselective hydrogenation of the corresponding *N*-acyl protected dehydro-β-amino acid derivative (enamine) using a homogeneous chiral catalyst.[2] However, this method typically requires prior separation of the (*Z*)- and (*E*)-enamine isomers from generally poorly selective mixtures to obtain this high enantioselectivity.[3] Also, removal of the *N*-acyl protecting group to access free β-aminoesters and amides after hydrogenation is difficult. An alternative route is the heterogeneous diastereoselective hydrogenation of chiral enamines produced from β-ketoesters and chiral benzylamines followed by hydrogenolysis of the benzyl group. The limited examples of auxiliary-based hydrogenation methods appearing in the literature proceed with low to moderate selectivity (<80% de).[4] Despite this, the heterogeneous approach offers numerous advantages: ease in separation of product from catalyst, low catalyst cost, catalyst reuse/recovery, and facile catalytic deprotection. Consequently, there is still a great impetus to develop asymmetric processes which employ heterogeneous catalysts. Toward this end, we have developed a diastereoselective heterogeneous catalytic system that converts enamines derived from β-ketoesters and amides and chiral phenylglycine amide (PGA) to β-amino acid derivatives in up to 99% de (200:1 selectivity). This approach has been applied to a variety of PGA-enamines affording stereoselectivities that are the highest ever reported for heterogeneous catalysts and are comparable to those of the best homogeneous catalysts.

We chose to explore the utility of the new chiral amine, (*S*)-phenylglycine amide (PGA) (Table 1), as a chiral auxiliary.[5] We anticipated that the carboxamide functionality on phenylglycine amide would serve as an additional point of coordination with the heterogeneous catalyst to give a more ordered hydrogenation transition state leading to higher diastereoselectivity. The (*S*)-PGA-enamine esters and amides (**2a**−**k**, Table 1) were prepared by stirring the corresponding β-ketoesters and amides with (*S*)-PGA in methanol or 2-propanol in the presence of catalytic amounts of acetic acid.[6] In all examples studied, only the (*Z*)-enamine isomer crystallized allowing isolation of the enamine in high geometrical purity. The ORTEP diagram of **2b** confirms the (*Z*)-enamine geometry (Figure 1). Of note is the hydrogen bond between the β-enamine proton and the carbonyl functionalities of the carboxamide and methyl ester, which helps to stabilize the *Z*-isomer in preference to the *E*-isomer.

With a convenient method for preparing the PGA-derived enamines, we next sought to identify a heterogeneous catalyst. Preliminary screening indicated that platinum oxide (PtO_2, Adam's catalyst) in THF was the most active and selective catalyst for this

Table 1. Diastereoselective Hydrogenation of (*Z*)-**2**



entry	2	PtO_2[a] (mol %)	additive[b] (mol %)	time	yield[c] [conv][e]	de (%)[f]
1	**2a**	uw (10)		3 h	[12%]	92
2	**2a**	uw (10)	A (100)	3 h	[100%]	95
3	**2a**	uw (10)	A (300)	3 h	[100%]	90
4	**2a**	aw (10)		3 h	[97%]	97
5	**2a**	aw (10)	B (3)	4 h	[96%]	99
6	**2a**	aw (10)		8 h	87 (66)[d]	96 (3*R*)[g]
7	**2b**	aw (10)		2 d	94 (82)	97 (3*S*)
8	**2c**	aw (10)		2 d	96 (88)	98 (3*R*)
9	**2d**	aw (10)		1 d	97 (94)	98 (3*R*, 2*S*)
10	**2e**	aw (2.5)		12 h	99 (98)	99 (3*R*)
11	**2f**	aw (2.5)		1 d	96 (88)	97 (3*R*)
12	**2g**	aw (50)		2 d	[70%]	70 (3*S*)[h]
13	**2h**	aw (50)		3 d	85 (46)	88
14	**2i**	aw (50)		2 d	[24%]	78
15	**2j**	aw (10)		2 d	86 (80)	89
16	**2k**	aw (10)		2 d	96 (92)	97

[a] aw = acid washed, uw = unwashed. [b] A = acetic acid, B = triethylamine. [c] % assay yield. [d] % isolated yield (unoptimized). [e] Reaction conversion. [f] Determined by HPLC. [g] The absolute configuration determined after debenzylation to the free amine by comparing the sign of optical rotations. [h] Assigned from the X-ray structure.

hydrogenation.[7] A practical hydrogen pressure of 90 psi was used at 22 °C. Initially, the reaction was slow using 10 mol % PtO_2 (entry 1, Table 1). Acetic acid is often used to accelerate hydrogenations catalyzed by PtO_2 either by activating the catalyst by dissolving surface bound alkali metals[8] or by preventing deactivation of the catalyst by the product amine.[9] Addition of increasing amounts of acetic acid improved the rate (entries 2, 3) but resulted in a progressive decline in selectivity. We discovered that acetic acid in the reaction mixture was undesirable because it catalyzes isomerization to the less selective (*E*)-enamine.[10] To circumvent this, we developed a simple procedure involving washing the catalyst with acetic acid and thoroughly drying the

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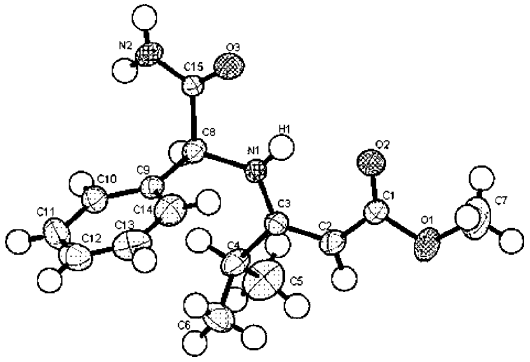

Figure 1. X-ray structure of **2b**.

solid after filtration.[11] Thus, not only is the washed catalyst more active than the unwashed catalyst, but it also significantly improved the diastereoselectivity in the hydrogenation (entry 1 vs 4). This catalyst still contained a small amount of residual acetic acid that led to some isomerization and loss in selectivity. Addition of a small amount of triethylamine, however, neutralized this acid and improved the selectivity to a very high 99% de with little impact on reaction rate (entry 5).

Using the acid washed catalyst, high selectivities were observed with a wide range of (*Z*)-enamine esters and amides (Table 1). The alkyl (R_1) tri- and tetra-substituted enamines (**2a**−**f**) showed the highest reactivity and selectivity (97−99% de). The relative stereochemistry was the same in all of these examples as indicated.[12] The aryl enamine esters (**2g**,**i**) were generally less reactive and selective as compared to the electron-rich aryl enamine ester (**2h**) and aryl enamine amides (**2j**,**k**) which displayed higher rates and selectivities.

Hydrogenolysis of **3a**−**f** (H_2, $Pd(OH)_2$/C, methanol, AcOH) readily afforded the free alkyl β-aminoesters and amides with 2-phenylacetamide. Hydrogenolysis of the arylamines (**3g**−**k**) was expected to be problematic under these conditions due to the presence of competing benzylic sites, and, in fact, **3g** afforded a mixture of the desired β-aminoester and a deaminated ester byproduct (56%).[6] Finally, the diastereoselective hydrogenation and debenzylation can be performed in one pot by simply adding $Pd(OH)_2$/C after the enamine hydrogenation with platinum oxide.

The high diastereoselectivities reported here are remarkable considering the structural complexity of Adam's catalyst[13] and the reduced Pt. The important role that the PGA carboxamide group plays is evident from the superior selectivities observed with PGA-derived enamines as compared to the α-methylbenzylamine-derived enamines[4] and suggests a strong interaction of this group with the catalyst surface. Invoking the classic Horiuti−Polanyi mechanism,[14] selective binding of the back face of the (*Z*)-enamines **2** to the catalyst surface, as directed by the coordinating PGA group, followed by hydrogen transfer from the catalyst to the bound face of **2** affords **3** with the observed stereochemistry. This diastereofacial discrimination is higher with the (*Z*)-enamines than with the *E*-isomers and is enhanced when activated catalyst is used with less alkali metal impurities present to inhibit hydrogen and substrate binding.

To gain further insight into the mechanism of this hydrogenation, a deuterium labeling study was performed. Reaction of **2a** with deuterium gas (90 psi D_2 for 8 h, acid washed PtO_2) afforded **3a** with deuterium incorporation at C2 (85%) and C3 (90%) and significant deuterium incorporation at the carboxamide NH_2 (∼60%). These results are consistent with direct reduction of the C═C bond as the major hydrogenation pathway[15] rather than via an initial isomerization to the imine tautomer followed by reduction of the C═N bond. Deuterium incorporation at the carboxamide NH_2 is consistent with coordination of this group to the catalyst surface, possibly via the π-orbitals in the conformation seen in the X-ray structure (Figure 1). In this model, the carboxamide binding with the bulky phenyl group of PGA disposed away from the metal surface enhances the diastereoface selective binding of the conjugated enamine system.

Thus, a new set of conditions was identified for the preparation of β-aminoesters and amides via heterogeneous catalysis with unprecedented diastereoselectivities and good substrate generality. This approach offers an alternative synthetic strategy to asymmetric hydrogenation methods.

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Supporting Information Available: Experimental details and crystallographic data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) PtO_2 (Engelhard, 15 g) was stirred 1 h in glacial acetic acid (50 mL) at room temperature. The catalyst was filtered, rinsed with glacial acetic acid (2 × 10 mL), and dried 1 day in a 50 °C vacuum oven. Analysis of the acetic acid wash showed significant levels of Na and K (∼5 μg each/mg of PtO_2).

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