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Enantioselective Synthesis of *anti*-β-Hydroxy-α-amido Esters via Transfer Hydrogenation

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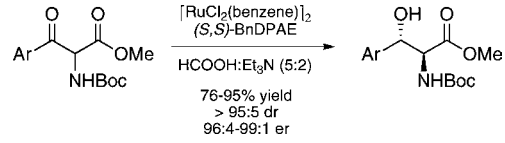
ABSTRACT



The asymmetric transfer hydrogenation of α-amido-*β*-keto esters to provide the corresponding *anti*-*β*-hydroxy-α-amido esters in good to excellent yields, diastereoselectivity, and enantioselectivity is reported. The procedure is operationally simple, and delicate handling of the catalyst is not necessary.

The significance of *β*-hydroxy-α-amino esters and their corresponding vicinal amino diols is confirmed by their prevalence in many biologically relevant natural products, pharmaceuticals, and peptides.[1] This structural motif appears in antibiotics such as vancomycin,[2] chloramphenicol, and the GE2270 thiopeptide family,[3] as well as in the HIV inhibitory papuamide family,[4] making the construction of this particular molecular constellation integral to many synthetic pursuits. Valuable chiral auxiliaries, catalysts, and building blocks are also readily accessible from *β*-hydroxy-α-amino esters and their derivatives.[5] Thus, the asymmetric synthesis of these scaffolds has received widespread attention in recent years.[6]

Dynamic kinetic resolution (DKR) of chirally labile α-amido or α-amino-*β*-keto esters using hydrogenation conditions has emerged as an efficient and powerful method for the formation of *β*-hydroxy-α-amino esters.[7] Under the current paradigm, hydrogenation of the *N*-acyl-protected α-amino-*β*-keto esters yields the *syn* diastereomer,[8] whereas the hydrochloride salt of α-amino-*β*-keto esters affords the *anti* diastereomer.[9] However, these methods often require high pressures and air-sensitive catalysts.[10] Furthermore, *β*-aryl-substituted *β*-hydroxy-α-amino esters are an important subclass of this biologically relevant scaffold, and these

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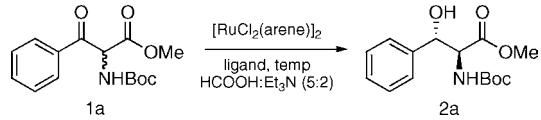
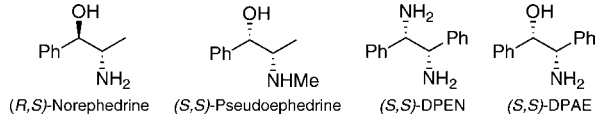
Table 1. Optimization of the ATH Reaction[a]



entry	arene dimer	ligand	temp	time	yield[b]	dr[c]	er[d]
1	*p*-cymene	(*S*,*S*)-TsDPEN	45 °C	24 h	100	92:8	58:42
2	*p*-cymene	(*R*,*S*)-norephedrine	45 °C	32 h	74	>95:5	60:40
3	*p*-cymene	(*S*,*S*)-pseudoephedrine	45 °C	24 h	86	>95:5	81:19
4	*p*-cymene	(*S*,*S*)- pseudoephedrine	rt	6 days	41	>95:5	82:18
5	benzene	(*S*,*S*)-pseudoephedrine	rt	6 days	62	>95:5	89:11
6	benzene	(*S*,*S*)-DPAE	rt	7 days	88	>95:5	90:10
7	benzene	(*S*,*S*)-TsDPAE	rt	11 days	60	>95:5	51:49
8	benzene	(*S*,*S*)-BnDPAE	rt	7 days	86	>95:5	95:5
9[e]	benzene	(*S*,*S*)-BnDPAE	rt	5 days	95	>95:5	97:3
10	benzene	(*R*,*S*)-BnDPAE	rt	10 days	98	>95:5	55:45



[a] Reactions preformed with 0.05 equiv of $[RuCl_2(arene)]_2$, 0.1 equiv of ligand heated in 2-propanol (c = 0.1 M) at 80 °C for 1 h. After cooling (if necessary), the catalyst was then added to the β-keto ester **1** (1 equiv) with $HCOOH:Et_3N$ (5:2) complex (c = 0.2 M). [b] Isolated yields. [c] >95:5 means that only a single diastereomer was visible in the ^1H NMR of the crude reaction mixture. [d] Determined by chiral HPLC. [e] Reactions run with 0.1 equiv of $[RuCl_2(arene)]_2$ and 0.2 equiv of ligand. DPEN = (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine. DPAE = (1*S*,2*S*)-2-amino-1,2-diphenylethanol. BnDPAE = (1*S*,2*S*)-2-(benzylamino-1,2-diphenylethanol).

substrates are traditionally more difficult to access with high enantioselectivity and diastereoselectivity using other routes such as phase transfer catalysis or asymmetric amino hydroxylation.[11]

Herein, we report a convenient and operationally simple alternative to these methods using the relatively unexplored DKR of α-amido-β-keto esters under asymmetric transfer hydrogenation (ATH) conditions.[12] This procedure yields the *anti*-β-hydroxy-α-amido esters and to our knowledge is the first report of accessing the *anti* diastereomer using ATH. This reduction proceeds under mild conditions without delicate handling of the catalyst. As the diastereoselectivity differs with the traditional hydrogenation methods, we also provide a stereochemical induction model based on our results as a valuable tool for the prediction of the diastereofacial selectivity when using ATH.

We began our investigations on the reduction of *N*-Boc-protected α-amido-β-keto ester **1a**, which had been reported to give the *syn* diastereomer under transfer hydrogenation conditions.[12a] Similar substrates have also given the *syn*

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(9) Synthesis of *anti*-β-hydroxy-α-amino esters: (a) Hamada, Y.; Makino, K. Stereoselective Synthesis of *anti*-β-Hydroxy-α-Amino Acids Using *anti*-Selective Asymmetric Hydrogenation. In *Asymmetric Synthesis and Application of α-Amino Acids*; American Chemical Society: Washington, D.C., 2009; Vol. 1009, pp 227−238. (b) Hamada, Y.; Koseki, Y.; Fujii, T.; Maeda, T.; Hibino, T.; Makino, K. *Chem. Commun.* **2008**, 6206–6208. (c) Makino, K.; Iwasaki, M.; Hamada, Y. *Org. Lett.* **2006**, *8*, 4573–4576. (d) Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784–5785. (e) Mordant, C.; Dunkelmann, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Chem. Commun.* **2004**, 1296–1297. (f) Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Eur. J. Org. Chem.* **2004**, 3017–3026. (g) Genet, J. P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555–567.

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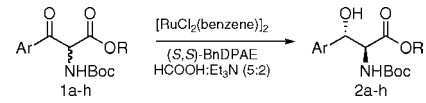
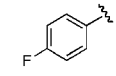
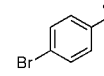
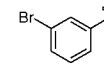
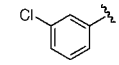
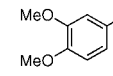
diastereomer under hydrogenation conditions.[13] Noyori's TsDPEN ligand, which has found great versatility in both ATH and asymmetric hydrogenation reactions, was examined first.[14] To our surprise we obtained the *anti*-β-hydroxy-α-amido ester **2a** in excellent yield and diastereoselectivity but poor enantioselectivity (Table 1, entry 1).[15] Intrigued by the *anti* diastereoselectivity of the reaction, we opted to further explore the reaction conditions to improve the enantioselectivity. Thus, we examined vicinal amino alcohols as ligands for the hydrogenation as these have been reported to give improved enantioselectivities.[16] Norephedrine did not give an increase in the enantioselectivity, but with pseudoephedrine a promising 82:18 er was observed (entries 2 and 3). Lowering the reaction temperature slightly increased the enantioselectivity at the price of the reaction time and yield (entry 4). Use of the less hindered $[RuCl_2(benzene)]_2$ precatalyst instead of $[RuCl_2(p\text{-cymene})]_2$ improved both the conversion and the enantioselectivity (entry 5).[16] Switching to the (*S*,*S*)-DPAE amino alcohol backbone gave better yields, and the Bn-protected DPAE ligand gave the best enantioselectivites and yields (entries 6−9).[17] Changing the catalyst loading to 20 mol % $[RuCl_2(benzene)]_2$ increased the yield moderately and slightly shortened the reaction time (entry 9).[18] The *R*,*S*-DPAE ligand gave a high yield but little enantioselectivity (entry 10).

With optimized conditions in hand, we wanted to examine the scope of the reaction. We surveyed a variety of aromatic substrates **1a**−**h**. The reaction conditions are tolerant to a wide variety of substitution patterns on the aryl moiety, giving good yields and excellent enantioselectivities in most cases (Table 2, entries 1−6 and 8). The *syn* diastereomer was not detected in any of the crude reaction mixtures. The ortho-substituted aromatic ketones gave excellent enantioselectivities, and this is the first report of DKR of ortho-substituted subtrates in the context of β-hydroxy-α-amino esters (entries 2 and 3).[19] Interestingly the 3-chloro substrate gave poor enantioselectivity, while the 3-bromo substrate gave excellent enantioselectivity and notably higher yield (entries 6 and 7).

Central to the utility of ketone reductions is the ability to predict and rationalize the stereochemical outcome. Here we propose a stereochemical model in which the observed diastereofacial discrimination can be rationalized by invoking

Table 2. Exploration of Substrate Scope



entry	Ar, R	1	2	yield[b]	er
1	 , Me	**a**	**a**	95	97:3
2	 , Et	**b**	**b**	83	99:1
3	 , Et	**c**	**c**	76	99:1
4	 , Et	**d**	**d**	89	96:4
5	 , Et	**e**	**e**	81	98:2
6	 , Et	**f**	**f**	94	96:4
7	 , Et	**g**	**g**	69	66:34
8	 , Et	**h**	**h**	95	97:3

[a] Reactions preformed with 0.1 equiv of $[RuCl_2(benzene)]_2$, 0.2 equiv of *S*,*S*-BnDPAE heated in 2-propanol (c = 0.1 M) at 80 °C for 1 h. After cooling, the catalyst was then added to the β-keto ester **1** (1 equiv) with $HCOOH:Et_3N$ (5:2) complex (c = 0.2 M) and stirred for 5−7 days at ambient temperature. Only a single diastereomer was visible in the ^1H NMR of the crude reaction mixture. [b] Isolated yields. [c] Determined by chiral HPLC.

a cyclic intermediate with a hydrogen bond between the *N*-H and the carbonyl moiety (Scheme 1, structure **B**) with subsequent hydride addition from the least hindered face of the carbonyl.[20] In line with this hypothesis are the results obtained from the reduction of the doubly protected *N*-Me, *N*-Boc analogue **3**, which is reduced to amino alcohol **4** in 82% yield and 72:28 dr in favor of the *syn* diastereomer (97:3 er).[21] Similar observations have been reported for the ATH of α-methoxy-β-keto esters,[22] *N*-Me, *N*-Cbz protected α-amido-β-keto esters,[12b] and α-alkyl-β-ketomamides,[23] all substrates which cannot form intramolecular hydrogen bonded intermediates corresponding to **B**, and for which the *syn* diastereomers are obtained as the major product.[24] Hence the ability to form an intramolecular hydrogen bond influences the diastereofacial selection and offers a consequent and diastereodivergent approach to these amino alcohols by

(13) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–55.

(14) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406.

(15) The relative stereochemistry was determined by conversion to the corresponding oxazolidinone and ^1H NMR analysis of the relevant *J* coupling values. See: (a) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153–2156.

(16) (a) Everaere, K.; Mortreux, A.; Bulliard, M.; Brussee, J.; van der Gen, A.; Nowogrocki, G.; Carpentier, J.-F. *Eur. J. Org. Chem.* **2001**, 275–291. (b) Everaere, K.; Carpentier, J.-F.; Mortreux, A.; Bulliard, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4083–4086.

(17) No reaction occurred in the absence of the $HCOOH:Et_3N$ (5:2) complex.

(18) Running the reaction for only two days and 20 mol % catalyst yielded the product in 55% yield and 96:4 er.

(19) Ortho-substituted aromatics are not reported in any of the references 9. However, ortho-substituted aromatic ketones have been reduced using ATH. For an example, see: Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 3788–3791.

(20) (a) Restorp, P.; Somfai, P. *Org. Lett.* **2005**, *7*, 893–895. (b) Kiyooka, S.-i.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958–1960.

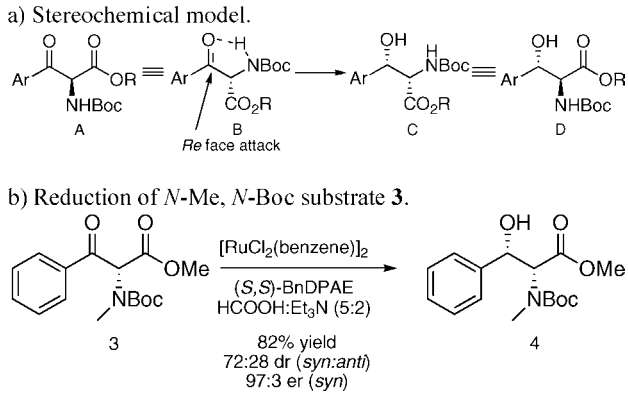
(21) The absolute stereochemistry has not been determined.

(22) Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 3788–3791.

(23) Limanto, J.; Krska, S. W.; Dorner, B. T.; Vazquez, E.; Yoshikawa, N.; Tan, L. *Org. Lett.* **2010**, *12*, 512–515.

(24) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920–2930.

Scheme 1. Rationalization of Observed Diastereoselectivity: (a) Stereochemical Model and (b) Reduction of *N*-Me, *N*-Boc Substrate **3**



simple selection of the appropriate catalyst and α-amido-*β*-keto ester precursor.

In conclusion, we have developed an operationally straightforward synthesis of *β*-hydroxy-α-amido esters using transfer hydrogenation of the corresponding α-amido-*β*-keto esters. This reaction proceeds in excellent enantioselectivities and diastereoselectivities to the *anti*-amino alcohol. The observed diastereoselectivity can be rationalized by hydrogen bonding between the *N*-H and the carbonyl moiety. The use of an *N*-Boc, *N*-alkyl doubly protected analogue, affords the *syn*-amino alcohol in support of this hypothesis and allows for diastereodivergent access to this class of compounds. Further exploration and exploitation of this technology is ongoing.

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Supporting Information Available: Detailed experimental procedures and ^{1}H and ^{13}C spectra are available for **1a**−**h**, **2a**−**h**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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