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Asymmetric Transfer Hydrogenation Coupled with Dynamic Kinetic Resolution in Water: Synthesis of *anti*-β-Hydroxy-α-amino Acid Derivatives

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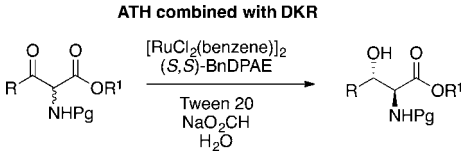
ABSTRACT



The use of asymmetric transfer hydrogenation combined with dynamic kinetic resolution for the synthesis of β-hydroxy-α-(*tert*-butoxycarbonyl)-amino esters in water is described. This procedure provides the desired amino alcohols in good yields, diastereoselectivities, and enantioselectivities. A surfactant is employed to achieve good yields due to the hydrophobic nature of both the catalyst and substrate. The reaction setup is operationally simple, and nondegassed water can be used as the solvent.

The development of methods for the stereoselective construction of β-hydroxy-α-amino acids and their derivatives is of signifiant interest due to the high frequency of such architectures in natural products and pharmaceuticals. For example, this particular molecular arrangement is found in sphingosine,[1] cyclomarin C,[2] the papuamides,[3] the thiopeptide antibiotic, GE2270A,[4] and vancomycin,[5] all of which possess important biological properties. Furthermore, derivatives of these compounds can also be used as chiral auxiliaries and chiral building blocks.[6]

An elegant approach to the desired chiral subunits is the asymmetric transfer hydrogenation (ATH)[7] or asymmetric hydrogenation (AH)[8] of configurationally labile β-keto-esters bearing an α nitrogen substituent. Such a reaction sequence proceeds through a dynamic kinetic resolution (DKR) and sets the configuration of both stereocenters.[9]

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(1) (a) Llaveria, J.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Org. Lett.* **2008**, *11*, 205–208. (b) Torssell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643–1646. (c) van den Berg, R. J. B. H. N.; van den Elst, H.; Korevaar, C. G. N.; Aerts, J. M. F. G.; van der Marel, G. A.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2011**, *2011*, 6685–6689.

(2) (a) Hamada, Y.; Shioiri, T. *Chem. Rev.* **2005**, *105*, 4441–4482. (b) Wen, S.-J.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2721–2724.

(3) Ford, P. W.; Gustafson, K. R.; McKee, T. C.; Shigematsu, N.; Maurizi, L. K.; Pannell, L. K.; Williams, D. E.; Dilip de Silva, E.; Lassota, P.; Allen, T. M.; Van Soest, R.; Andersen, R. J.; Boyd, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 5899–5909.

(4) Nicolaou, K. C.; Dethe, D. H.; Leung, G. Y. C.; Zou, B.; Chen, D. Y.-K. *Chem.—Asian J.* **2008**, *3*, 413–429.

(5) (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152. (b) Girard, A.; Greck, C.; Ferroud, D.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 7967–7970.

(6) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–876.

(7) (a) Mordant, C.; Dunkelmann, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Chem. Commun.* **2004**, 1296–1297. (b) Mohar, B.; Valleix, A.; Desmurs, J.-R.; Felemez, M.; Wagner, A.; Mioskowski, C. *Chem. Commun.* **2001**, 2572–2573. (c) Xu, Z.; Zhu, S.; Liu, Y.; He, L.; Geng, Z.; Zhang, Y. *Synthesis* **2010**, 811–817.

(8) (a) Makino, K.; Iwasaki, M.; Hamada, Y. *Org. Lett.* **2006**, *8*, 4573–4576. (b) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 2816–2828. (c) Hamada, Y.; Koseki, Y.; Fujii, T.; Maeda, T.; Hibino, T.; Makino, K. *Chem. Commun.* **2008**, 6206–6208. (d) 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: 2009; Vol. 1009, pp 227–238.

(9) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327.

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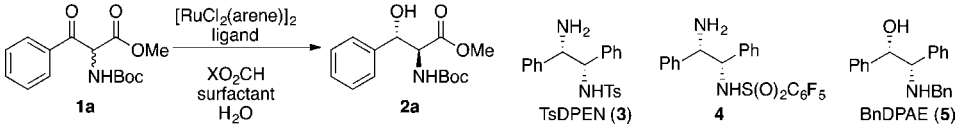
Table 1. Optimization of the ATH via DKR Reaction of **1a**



entry	method[a]	arene/ligand	surfactant (equiv)	XO_2CH (equiv)	temp (°C)/time	yield[b]	dr[c]	er[d]
1	A	*p*-cymene/**3**	–	NaO_2CH (5 equiv)	20 °C/16 h	<5%	–	–
2	A	*p*-cymene/**3**	SDS (0.5 equiv)	NaO_2CH (15 equiv)	30 °C/16 h	50%	16:1	77:23
3	A	*p*-cymene/**3**	SDS (0.1 equiv)	NaO_2CH (15 equiv)	30 °C/16 h	31%	–	–
4	A	*p*-cymene/**3**	SDS (1 equiv)	NaO_2CH (15 equiv)	30 °C/16 h	18%	–	–
5	A	*p*-cymene/**3**	SDS (0.5 equiv)	LiO_2CH (15 equiv)	30 °C/16 h	80%	7:1	55:45
6	A	*p*-cymene/**3**	SDS (0.5 equiv)	KO_2CH (15 equiv)	30 °C/16 h	46%	16:1	70:30
7	A	*p*-cymene/**3**	SDS (0.5 equiv)	NaO_2CH (5 equiv)	30 °C/16 h	26%	20:1	93:7
8	A	*p*-cymene/**3**	SDS (0.5 equiv)	NaO_2CH (5 equiv)	30 °C/3 d	24%	21:1	–
9	B	*p*-cymene/**3**	SDS (0.5 equiv)	NaO_2CH (5 equiv)	30 °C/16 h	70%	9:1	86:14
10	B	*p*-cymene/**4**	SDS (0.5 equiv)	NaO_2CH (5 equiv)	30 °C/16 h	54%	9:1	66:33
11	B	benzene/**5**	SDS (0.5 equiv)	NaO_2CH (5 equiv)	30 °C/16 h	28%	14:1	96:4
12	B	benzene/**5**	CTAB (0.5 equiv)	NaO_2CH (5 equiv)	30 °C/16 h	30%	7:1	93:7
13	B	benzene/**5**	Tween 20 (0.2 equiv)	NaO_2CH (5 equiv)	30 °C/16 h	82%	12:1	96:4
14	B	benzene/**5**	Tween 20 (0.2 equiv)	NaO_2CH (5 equiv)	20 °C/3 d	80%	13:1	97:3
15[e]	B	benzene/**5**	Tween 20 (0.2 equiv)	NaO_2CH (5 equiv)	20 °C/3 d	81%	12:1	96:4

[a] **A**: $[RuCl_2(p\text{-cymene})]_2$ (3 mol %) and (*S,S*)-TsDPEN (10 mol %) were mixed for 1 h at 30 °C in degassed water. Then the substrate (1 equiv), SDS (equiv given), and formate salt (equiv given) were added, and the reaction was heated at 30 °C. **B**: $[RuCl_2(arene)]_2$ (3 mol %) and (*S,S*)-ligand (10 mol %) were mixed for 1 h at 40 °C in CH_2Cl_2. The CH_2Cl_2 was removed, and then the substrate (1 equiv), surfactant (equiv given), NaO_2CH (5 equiv), and degassed water were added; the reaction was heated at 30 or 20 °C. [b] Isolated yields of products after flash chromatography. [c] The diastereomeric ratio was measured by ^1H NMR. [d] The enantiomeric ratio was measured by chiral HPLC. [e] Deionized water, not degassed water.

We have recently applied this strategy to the construction of *anti*-β-hydroxy-α-(*tert*-butoxycarbonyl)amino esters in water/CH_2Cl_2 emulsions with NaO_2CH as the reducing agent.[10] Given the broad substrate scope of this reaction in a two-solvent emulsion, we became interested in exploring the possibility of omitting the organic solvent and utilizing only water. Water is the preferred solvent, because it is economical, nontoxic, nonflammable, and readily obtainable.[11] Such a reaction sequence is, therefore, desirable as it would provide a greener approach to these valuable compounds. A number of protocols for the ATH of ketones and imines in water have been developed, and this is a topic that has received much attention in recent years.[12] However, for the related ATH coupled DKR reactions, methods using water as the solvent are scarce. Furthermore, although ATH of water insoluble ketones that are liquid under the reaction conditions is well-known, fewer reports of ATH in water for solid ketones have been disclosed. Herein, we report our results toward ATH via DKR in water of solid ketones.

Inspired by the results of Xiao in which ATH is performed on water and in air, we attempted to reduce ketone **1a** using similar conditions (Table 1, entry 1).[13] Surprisingly for ketone **1a** less than 5% conversion was observed and the substrate and catalyst formed an aggregate in the water. Unlike many of the previously reported ketone and imine substrates explored in ATH in aqueous media, **1a** is not water-soluble and is a solid at the reaction temperature (mp = 96 °C).[14,10] We then opted to explore the use of a surfactant to overcome the low reactivity of **1** in water.[12b,g,15] Gratifyingly, by introducing 0.5 equiv of SDS (Sodium dodecyl sulfate), we were able to isolate **2a** in 50% yield and 77:23 er (entry 2). Testing various amounts of surfactant revealed that 0.5 equiv of SDS was best (entries 2–4).

(10) (a) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274–5277. (b) Seashore-Ludlow, B.; Villo, P.; Somfai, P. *Chem.—Eur. J.* **2012**, 7219–7223.

(11) (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302–6337. (c) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772.

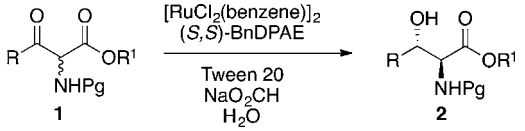
(12) (a) Wang, C.; Wu, X.; Xiao, J. *Chem.—Asian J* **2008**, *3*, 1750–1770. (b) Wang, F.; Liu, H.; Cun, L.; Zhu, J.; Deng, J.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 9424–9429. (c) Wang, C.; Li, C.; Wu, X.; Pettman, A.; Xiao, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524–6528. (d) Ariger, M. A.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 4522–4524. (e) Tang, L.; Lin, Z.; Wang, Q.; Wang, X.; Cun, L.; Yuan, W.; Zhu, J.; Deng, J. *Tetrahedron Lett.* **2012**, *53*, 3828–3830. (f) Liu, J.; Zhou, Y.; Wu, Y.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2008**, *19*, 832–837. (g) Ahlford, K.; Adolfsson, H. *Catal. Commun.* **2011**, *12*, 1118–1121. (h) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *5*, 2103–2106. (i) Li, J.; Tang, Y.; Wang, Q.; Li, X.; Cun, L.; Zhang, X.; Zhu, J.; Li, L.; Deng, J. *J. Am. Chem. Soc.* **2012**, *134*, 18522–18525.

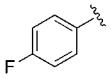
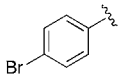
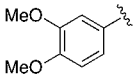
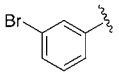
(13) (a) Wu, X.; Xiao, J. *Chem. Commun.* **2007**, 2449–2466. (b) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* **2004**, *2*, 1818–1821. (c) Wu, X.; Liu, J.; Di Tommaso, D.; Iggo, J. A.; Catlow, C. R. A.; Bacsa, J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 7699–7715.

(14) Wang, W.; Li, Z.; Mu, W.; Su, L.; Wang, Q. *Catal. Commun.* **2010**, *11*, 480–483.

(15) (a) Yin, L.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, *20*, 2033–2037. (b) Yin, L.; Shan, W.; Jia, X.; Li, X.; Chan, A. S. C. *J. Organomet. Chem.* **2009**, *694*, 2092–2095. (c) Rhyoo, H. Y.; Park, H.-J.; Suh, W. H.; Chung, Y. K. *Tetrahedron Lett.* **2002**, *43*, 269–272. (d) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6731–6734.

Table 2. Substrate Scope of the ATH via DKR Reaction[a]



entry	1/2	R	Pg, R^1	yield[b]	dr[c]	er[d]
1	**a**		Boc, Me	80%	13:1	97:3
2	**b**		Boc, Et	83%	20:1	97:3
3	**c**		Boc, Et	82%	13:1	95:5
4	**d**		Boc, Et	79%	14:1	98:2
5	**e**		Boc, Et	84%	15:1	89:11
6	**f**		Boc, Et	78%	14:1	98:2
7	**g**		Boc, Et	85%	7:1	94:6
8	**h**		CBz, Me	80%	23:1	96:4
9[e]	**i**		CBz, Et	72%	9:1	97:3
10	**j**		CBz, Me	68%	20:1	89:11[f]

[a] $[RuCl_2(benzene)]_2$ (3 mol %) and (*S,S*)-BnDPAE (10 mol %) were mixed for 1 h at 40 °C in CH_2Cl_2. The CH_2Cl_2 was removed, and then the substrate (1 equiv), surfactant (equiv given), NaO_2CH (5 equiv), and water were added; the reaction was run at ambient temperature for 72 h. [b] Isolated yield. [c] Measured by ^1H NMR [d] Measured by chiral HPLC. [e] $[RuCl_2(p\text{-cymene})]_2$ (3 mol %) and (*S,S*)-TsDPEN (10 mol %) were used. [f] Er determined by Mosher ester method. See Supporting Information.

We then examined the effect of the counterion on the hydrogen source to see if this would impact the yield and enantioselectivity. This revealed a dependence on the counterion for both the reaction yield and enantioselectivity. It was found that LiO_2CH gave a higher yield but distinctly lower enantioselectivity (compare entries 2 and 5). KO_2CH gave similar results to NaO_2CH; however a slightly lower enantioselectivity was obtained (compare entries 2 and 6). We then decreased the amount of NaO_2CH as a means to increase the enantioselectivity. This had the desired effect, but the yield also decreased significantly (entry 7). Unfortunately, leaving the reaction for 3 days did not improve the yield (entry 8).

Disappointed by the low yields and enantioselectivities, we then investigated an alternative preparation of the catalyst, surmising that the active catalyst was inadequately formed in the previous protocol, or inefficiently enclosed within the micelle. We then preformed the catalyst in an organic solvent, which was removed prior to the addition of the water, substrate, surfactant, and reducing agent.[16] Immediately a boost in yield was observed, and significantly we could reduce the amount of reducing agent to 5 equiv of NaO_2CH, which enhanced the enantioselectivity (entries 2 and 9). Having finally achieved a reasonable yield, we then examined several other ligands in hopes of attaining superior enantioselectivity. FDPEN **4**, which had been previously reported for similar compounds, gave a low enantioselectivity.[17] Surprisingly, switching to BnDPAE (**5**) gave a markedly lower yield but an enantioselectivity within the desired range. This suggests that relatively small alterations in the ligand backbone can significantly impact the reactivity of the catalyst in water, even though the catalysts provide comparable yields in triethylammonium formate (5:2) azeotrope.[10b] We then hypothesized that the low yield in the reaction with BnDPAE could be due to the charge interactions between the surfactant and the formate. In previous studies a positively charged surfactant was found to perform best.[12b] However, testing CTAB (hexadecyltrimethylammonium bromide) again resulted in low yields and enantioselectivities. Interestingly, employing a neutral surfactant, Tween 20 (Polyoxyethylene (20) sorbitan monolaurate), resulted in both good yields and enantioselectivities.[18] Presumably the use of the neutral surfactant allows for the formate salt to easily enter the micelles. Running the reaction at ambient temperature for a longer period of time gave slightly increased enantio- and diastereoselectivities. Furthermore, using deionized, but not degassed, water gave equivalent results, further simplifying the reaction procedure.

With working conditions in hand, we then wanted to investigate the substrate scope of the ATH via a DKR reaction in water. In general this method gives high yields, diastereoselectivities, and enantioselectivities for a broad range of substrates. Substitution at the *para* position is well tolerated (Table 2, entries 2–4), as well as electron-rich and -poor substrates (entries 2, 4, 6). The 3-bromo substrate **1e** gave a good yield and diastereoselectivity, but the enantioselectivity was rather poor (entry 5).[19] A low enantioselectivity for the 3-chloro-substituted substrate had been observed in our previous work, although the 3-bromo-substituted substrate yielded high enantioselectivities under these conditions.[10] 2-Substition of the aromatic group was also well tolerated (entry 6). Both the heteroaromatic substrate **1g** and alkenyl substrate **1h** gave good yields, diastereoselectivities, and enantioselectivities (entries 7 and 8). The alkyl substrates **1i** and **1j** both gave slightly lower

(16) The reactions were run under N_2 as irreproducible results were obtained when the reactions were run in air.

(17) Liu, Z.; Shultz, C. S.; Sherwood, C. A.; Krska, S.; Dormer, P. G.; Desmond, R.; Lee, C.; Sherer, E. C.; Shpungin, J.; Cuff, J.; Xu, F. *Tetrahedron Lett*. **2011**, *52*, 1685–1688.

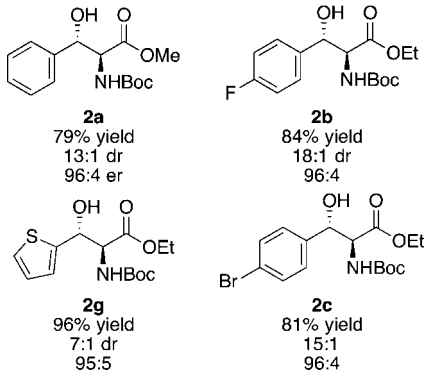
(18) Due to the large molecular weight of Tween 20, 20 mol % of this surfactant is equivalent in weight to 50 mol % SDS or CTAB.

(19) We also tried halving the amount of NaO_2CH to increase the enantioselectivity, but the enantioselectivity remained poor.

yields, and the enantioselectivity of the **2j** was poor (entries 9 and 10). This could be due to the steric bulk of the *tert*-butyl moiety, as increased steric bulk is known to decrease the enantioselectivity in ATH reactions.[12b]

Given the success of the above method for a broad range of substrates, we wondered if preparation of the catalyst in water with a surfactant would furnish similar results. Since such a procedure would completely obviate the need for an organic solvent, we investigated a protocol where the ruthenium precatalyst, (*S*,*S*)-BnDPAE, and Tween 20 were stirred in water, followed by the addition of the substrate and reducing agent. Gratifyingly, essentially identical results were obtained for the reduction of substrate **1a** into product **2a** (Scheme 1; compare Table 1, entry 13). To verify the applicability of this method we reexamined several other substrates **1b**, **1g**, and **1c**. This provided the corresponding products **2b**, **2g**, and **2c** in comparable yields, enantioselectivities, and diastereoselectivities as before and confirmed the generality of this method (compare Table 2).

Scheme 1. Results for ATH via DKR in Water with Catalyst Formed in Water with Surfactant[a]



[a] $[RuCl_2(benzene)]_2$ (3 mol %), (*S*,*S*)-BnDPAE (10 mol %), and Tween 20 (20 mol %) were mixed for 1 h at 40 °C in water. Then the substrate (1 equiv) and NaO_2CH (5 equiv) were added, and the reaction was run at 30 °C for 24 h. Substrate **1g** resulting in product **2g** was run at ambient temperature for 72 h.

In conclusion, we have developed an efficient and practical method for the construction of *anti*-β-hydroxy-α-amino acid derivatives in water with a surfactant, removing the need for an organic solvent. This method gives high yields, diastereoselectivities, and enantioselectivities for a broad range of substrates, including aryl-, alkenyl-, and alkyl-subsituted β-ketoesters. Unlike previous reports, the use of high melting solids is tolerated, and because the reaction proceeds via a DKR, vicinal stereocenters are generated. Furthermore, we have uncovered a counterion effect in the reaction in negatively charged micelles and found that a neutral surfactant is best for the $[RuCl_2(benzene)]_2$ and (*S*,*S*)-BnDPAE catalyst combination. Our studies revealed that subtle differences in the ligand backbone greatly influence the activity of the catalyst in water, which should offer insight into further development of ATH via DKR in water.

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Supporting Information Available. Information regarding the preparation of **1a**−**1j** and **2a**−**2j** and ^1H spectra of **2a**−**2j** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.