Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective synthesis of *anti*-β-amido-α-hydroxy esters via asymmetric transfer hydrogenation coupled with dynamic kinetic resolution

Marvin Villacrez [a], Peter Somfai [a,b,*]

[a] Centre for Analysis and Synthesis, Lund University, PO Box 124, 221 00 Lund, Sweden
[b] Institute of Technology, University of Tartu, Nooruse 1, 504 41 Tartu, Estonia

ARTICLE INFO

Article history:
Received 18 June 2013
Revised 6 July 2013
Accepted 19 July 2013
Available online xxxx

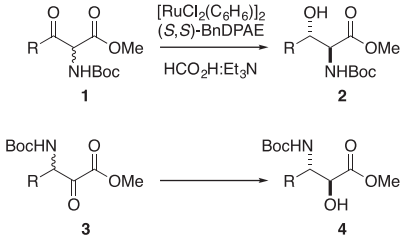
Keywords:
Dynamic kinetic resolution
Asymmetric transfer hydrogenation
Ruthenium
Enantioselective
1,2-Amino alcohols

ABSTRACT

The asymmetric transfer hydrogenation of β-amido-α-keto esters providing the corresponding *anti*-β-amido-α-hydroxy esters via dynamic kinetic resolution is reported. The use of a commercially available, or simply prepared, chiral ruthenium catalyst results in good yields as well as high diastereoselectivities and enantioselectivities.

The β-amino-α-hydroxy ester functionality, and the related vicinal amino alcohol moiety, are found in a variety of biologically active natural products.[1] The importance of 1,2-amino alcohols is also well recognized in asymmetric synthesis, where the need for chiral auxiliaries and ligands is continuously increasing.[2] Not surprisingly, the asymmetric synthesis of these structures has received considerable attention.[3]

It has been shown that asymmetric transfer hydrogenation (ATH) coupled with dynamic kinetic resolution (DKR)[4] can be applied to the formation of α-substituted-β-hydroxy esters.[5] In addition, we have previously shown that ATH/DKR of α-amido-β-keto esters **1** offers an efficient entry to *anti*-α-amido-β-hydroxy esters (Scheme 1).[6] This strategy relies on the stereochemical lability of the α-stereocenter in **1**, allowing for two stereocenters to be introduced in the asymmetric reduction. The β-amido-α-hydroxy ester **4** could, in theory, be obtained from **3** using a similar ATH/DKR approach, thus accessing the regioisomeric amino alcohol derivatives. The realization of such a strategy would depend on the rate of racemization of the β-stereocenter in substrate **3**, which must be faster than the rate of transfer hydrogenation. Although this kinetic scenario is indeed operating in the ATH/DKR of ester **1**, it is not obvious that it should also hold true for regioisomer **3**, in which the rate of racemization would be expected to be lower than that in **1**.



Scheme 1.

In an elegant study, Johnson and co-workers demonstrated that β-alkyl-substituted α-keto esters can be reduced using ATH/DKR to the corresponding β-alkyl-substituted α-hydroxy esters in high yield, distereoselectivity, and enantioselectivity, thus lending considerable support for the proposed conversion of ketone **3** into amido alcohol **4**.[7] More recently, the Johnson group reported the asymmetric synthesis of compound **4** from **3** using an asymmetric transfer hydrogenation coupled with kinetic resolution,[8] which prompted us to report our findings in this area. Herein, we report our results on the enantioselective synthesis of *anti*-β-amido-α-hydroxy esters via ATH/DKR.

We began our investigation of the ATH/DKR of β-amido-α-keto-esters by subjecting substrate **5a**[9] and $[RuCl_2(cymene)]_2$ to a series of 1,2-diphenylethane-1,2-diamine (DPEN) and 2-amino-1,2-diphenylethanol (DPAE) derived chiral ligands in DMF using HCO_2-

* Corresponding author. Tel.: +46 70 6936377; fax: +46 46 2228209.
E-mail address: peter.somfai@chem.lu.se (P. Somfai).

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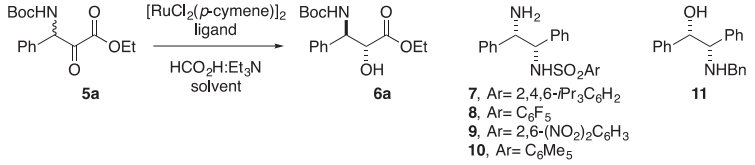
http://dx.doi.org/10.1016/j.tetlet.2013.07.100

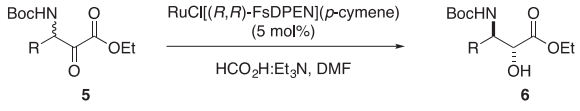
Table 1
Asymmetric transfer hydrogenation of **5a**[a]



Entry	Ligand	Solvent	Yield[b] (%)	Time (h)	dr[b]	er[c]
1	**7**	DMF	95	1	>20:1	94:6
2	**8**[d]	DMF	95	1	>20:1	95:5
3	**9**	DMF	73	5	>20:1	78:22
4	**10**	DMF	97	1	>20:1	81:19
5	**11**	DMF	88	0.5	>20:1	83:17
6	**8**[d]	Toluene	90	1	>20:1	90:10
7	**8**[d]	DMSO	94	1	>20:1	94:6
8	**8**[d]	Et_3N:HCO_2H (2:5)	93	1	>20:1	92:8
9[e]	**8**[d]	H_2O:CH_2Cl_2	95	1	3:1	n.d.[f]

[a] Reactions performed by heating $[Ru(cymene)Cl_2]_2$ (0.05 equiv) and the ligand (0.15 equiv) in 2-propanol (*c* 0.1 M) at 80 °C for 1 h. After cooling to rt the solvent was removed and the catalyst was added to a solution of **5a** (1 equiv, *c* 0.1 M) and HCO_2H/Et_3N (5:2, 5 equiv).
[b] Yield and dr determined by ^1H NMR spectroscopy of the crude reaction mixture.
[c] Determined by chiral HPLC analysis of the crude reaction mixture.
[d] Commercially available RuCl[(*R*,*R*)-FsDPEN](*p*-cymene) was used.
[e] Reaction was performed using emulsion conditions, see Ref. 6b.
[f] Not determined.

Table 2
Substrate scope of the ATH/DKR reaction[a]



Entry	**5**, R=	Yield[b] (%)	Time (h)	er[c]
1	**a**, Ph	95	1	95:5
2	**b**, *p*-$MeOC_6H_4$	96	1	98:2
3	**c**, *p*-MeC_6H_4	96	1	94:6
4	**d**, *p*-FC_6H_4	89	2	99:1
5	**e**,*o*-BrC_6H_4	78	2	94:6
6	**f**, *m*-BrC_6H_4	68	2	62:38
7	**g**, 3-Thienyl	92	1	94:6

[a] To a solution of the substrate (1 equiv) in DMF (*c* 0.1 M) was added RuCl[(*R*,*R*)-FsDPEN](*p*-cymene) (5 mol %) and HCOOH/Et_3N (5:2, 5 equiv), and the resultant mixture was stirred at rt for the indicated time.
[b] Yield and dr (>20:1 in each case) determined by ^1H NMR spectroscopy of the crude reaction mixture.
[c] Determined by chiral HPLC analysis of the crude reaction mixture.

H:Et_3N as the reducing agent (Table 1, entries 1–5). In all cases the corresponding β-amido-α-hydroxy ester **6a** was obtained in good yield and excellent diastereoselectivity, favouring the *anti* diastereomer.[10] The optimal conditions used the pentafluorinated DPEN derivative **8** as ligand, affording **6a** in 95:5 er (Table 1, entry 2).[11] Next, the influence of changing the solvent on the reaction outcome was investigated, but solvents other than DMF resulted in inferior results (entries 2 and 6–9). Several aspects of this reaction are noteworthy. Compared to the ATH/DKR of the regioisomeric α-amido-β-keto esters, which normally take 1–7 days to reach completion, the present transfer hydrogenation of **5a** reached completion within 1 h when conducted in DMF and using chiral ligand **8** (entry 2). This difference in reactivity is perhaps due to the increased electrophilicity of the α-carbonyl carbon in **5a** compared to that of the regioisomeric β-carbonyl derivative, resulting in a faster reduction. It was also noted that the dr of the reaction decreased upon prolonged reaction time, going from dr >20:1 (*anti*:*syn*) when the reaction was terminated after 1 h to 3:1 (*anti*:*syn*) when it was allowed to stand overnight. It is believed that this is the result of epimerization of the α-stereocenter under the reaction conditions and that the dr obtained after prolonged reaction times represents the equilibrium value under the present conditions. Furthermore, **6a** was not stable during purification by flash chromatography on silica gel resulting in a 40–50% isolated yield, compared to 95% yield as determined by ^1H NMR spectroscopy of the crude reaction mixture using an internal standard.

With the optimized conditions in hand the scope of the reaction was examined and the performance of several aromatic substrates **5a**–**g** was investigated (Table 2).[12] Both electron-rich (entries 2 and 3) and electron-poor (entry 4) aromatics performed well, affording the corresponding *anti*-amino alcohols as the only detectable diastereomer in good yields and high er. Somewhat surprisingly, the *m*-bromo derivative **5f** was reduced with only modest er, while the corresponding *o*-bromo compound **5e** yielded amino alcohol **6e** in high er. It was also noted that the heteroaromatic substrate **5g** was tolerated under the reaction conditions, affording **6g** in good yield and selectivity.

In conclusion, a rapid and straightforward diastereo- and enantioselective synthesis of *anti*-β-amido-α-hydroxy esters via ATH/DKR of the corresponding β-amido-α-keto esters has been developed. The present protocol makes use of a commercially available ligand–catalyst complex, thus making it easy and operationally straightforward to perform.

Acknowledgment

The authors would like to thank Lund University and the Estonian Ministry of Education (project no. SF0180073s08) for funding.

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9. Compounds **5a**–**g** were prepared according to known procedures, see: Zhao, Y.; Jiang, N.; Chen, S.; Peng, C.; Zhang, X.; Zou, Y.; Zhang, S.; Wang, J. *Tetrahedron* **2005**, *61*, 6546–6552.
10. The relative stereochemistry was determined by conversion into the corresponding oxazolidinone and ^{1}H NMR analysis of the relevant *J* coupling values. See: Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153–2156.
11. The absolute stereochemistry of **6a** was determined by comparing its optical rotation, $[\alpha]_D^{25}$ −82 (*c* 0.3, $CHCl_3$), with literature data, $[\alpha]_D^{25}$ −81.5 (*c* 0.3, $CHCl_3$); see Ref. 8.
12. *Typical experimental procedure:* Reduction of **5a**: A solution of **5a** (30 mg, 0.1 mmol) in DMF (1 mL) was transferred to a vial containing RuCl[(*R*,*R*)-FsDPEN](*p*-cymene) (3.5 mg, 4.9 μmol) After stirring for 10 min, HCO_2H/Et_3N (40 μL, 0.5 mmol) was added. Upon completion of the reaction, the mixture was diluted with Et_2O (5 mL) and H_2O (5 mL), the phases were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated. ^{1}H NMR analysis of the crude reaction mixture indicated a 95% yield (2-methoxynaphthalene as the internal standard). The residue was purified by flash chromatography (15% EtOAc:heptane) to give **6a** as a white solid (20 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H), 5.62–5.60 (d, *J* = 8.5 Hz, 1H), 5.12–5.10 (d, *J* = 8.5 Hz, 1H), 4.58 (br s, 1H), 4.19–4.07 (m, 2H), 2.90–2.89 (d, *J* = 6.7 Hz, 1H), 1.43 (s, 9H), 1.26–1.23 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 153.5, 130.1, 128.1, 129.7, 76.9, 73.1, 62.3, 55.5, 28.3, 14.1.