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Enantioselective synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters: application to the total synthesis of (+)-alexine†

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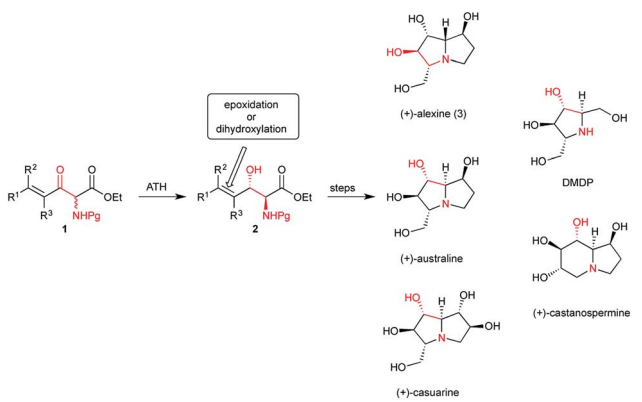
A straightforward synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters from the corresponding racemic α-amino-β-keto esters by using a ATH/DKR protocol has been developed. This method gives moderate to excellent yields with high chemo-, diastereo- and enantioselectivities for a broad range of substrates. In order to highlight the versatility of the methodology it was applied in an efficient asymmetric synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine.

β-Hydroxy-α-amino esters and their derivatives are important structural motif in a number of biologically relevant compounds.[1] As a consequence, several elegant methods have been developed for the stereoselective[2] and asymmetric[3] synthesis of such compounds. We speculated that the versatility of this scaffold could be expanded by the incorporation of a vinyl moiety in 3-position (*e.g.* **2**, Scheme 1), thus allowing for additional stereoselective manipulation. For example, stereoselective epoxidation[4] or dihydroxylation[5] of the carbon–carbon double bond in compound **2**, or cross metathesis, could furnish advanced such intermediates for the synthesis of polyhydroxylated alkaloids (Scheme 1), compounds with diverse biological activities.[6] Compound **2**, in turn, was excepted to be derived through a chemoselective asymmetric transfer hydrogenation (ATH) of α-amido-β-keto ester **1**. Herein we detail our efforts towards realizing this methodology and its application to the synthesis of (+)-alexine (**3**).



Scheme 1 Proposed route from α-amido- β-keto ester **1** to polyhydroxylated pyrrolizidine and indolizidine alkaloids.

ATH coupled with a dynamic kinetic resolution (DKR) of configurationally labile α-amido-β-keto ester has been proven to be a powerful method for the synthesis of *syn*- or *anti* β-hydroxy-α-amino esters.[7] In such transformation two contiguous stereocenters can be constructed in high er and dr in a single operation from a racemic starting material. We have previously developed a ATH process coupled with DKR for preparation aryl, alkyl or heterocyclic *anti*-β-hydroxy-α-amido ester in organic solvents, emulsions or water system.[8] For the present investigation it was of interest to expand the substrate scope to encompass substrates having an vinylic group in 3-position, *e.g.* compound **1**, and to investigate the possibility of developing a chemoselective 1,2-reduction of the carbonyl group in preference of a 1,4-reduction of the enone moiety.

The investigation was initiated by examining the ATH of ester **1a** using our previously optimized conditions ([$RuCl_2$(-benzene)]$_2$/(*S*,*S*)-BnDPAE), yielding a mixture of the desired *anti*-amino alcohol **2a**, having low dr and er, and the over-reduced compound **4** in poor selectivity (Table 1, entry 1). Subjecting **2a** to the reactions conditions did not afford **4** and it is believed that the latter compound is formed by an initial 1,4-reduction of the enone moiety in **1a** followed by a 1,2-reduction of the resultant carbonyl group. Screening of different ligands gave **2a** with increased diastereoselectivity, but in all cases the chemoselectivity remained low (entries 2–4). It was noted, however, that the use of (*S*,*S*)-DPAE resulted in the formation of **2a** in high enantiomeric excess (er 95 : 5, entry 4). It was then decided to explore different ruthenium dimer catalysts together with the (*S*,*S*)-DPAE ligand (entries 5–7). The use of ruthenium(II) dichloride dimer catalyst incorporating a substituted arene moiety resulted in an improved chemoselectivity with only traces of the over reduced compound **4** being observed, the best

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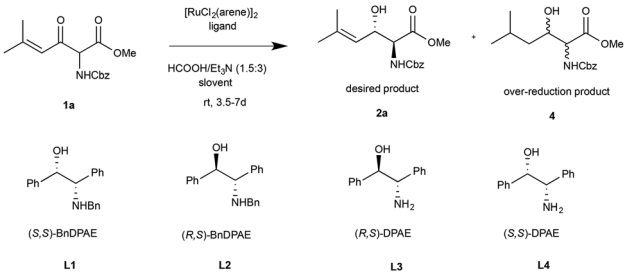
Table 1 Optimization of the ATH Reaction of **1a**[a]



Entry	Ru dimer	Ligand	Solvent	**1a**/**2a**/**4** (%)[b]	dr (*anti* : *syn*)[c]	er (*anti*)[d]
1	Benzene	**L1**	CH_2Cl_2	5/50/20	55 : 45	88.5 : 11.5
2	Benzene	**L2**	CH_2Cl_2	21/41/16	89 : 11	7 : 93
3	Benzene	**L3**	CH_2Cl_2	35/15/5	87 : 13	12.5 : 87.5
4	Benzene	**L4**	CH_2Cl_2	<5/52/20	80 : 20	95 : 5
5	*p*-Cymene	**L4**	CH_2Cl_2	33/47/<5	85 : 15	90.5 : 9.5
6	Mesitylene	**L4**	CH_2Cl_2	20/65/<5	91.5 : 8.5	93 : 7
7	Hexamethylbenzene	**L4**	CH_2Cl_2	34/28/<5	83 : 17	58 : 42
8	Mesitylene	**L4**	MeOH	49/24/<5	86 : 14	89.5 : 10.5
9	Mesitylene	**L4**	CH_3CN	26/37/<5	85 : 15	85 : 15
10	Mesitylene	**L4**	Dioxane	8/68/<5	93 : 7	95.5 : 4.5
11	Mesitylene	**L4**	$CHCl_3$	13/57/<5	94.5 : 5.5	96 : 4
12[e]	Mesitylene	**L4**	Dioxane	11/68/<5	93 : 7	96 : 4
13[f]	Mesitylene	**L4**	Dioxane	15/60/<5	94 : 6	96 : 4
14[g]	Mesitylene	**L4**	Dioxane	12/72/<5	95 : 5	96.5 : 3.5

[a] Reactions preformed with $[RuCl_2(arene)]_2$ (0.1 eq.) and ligand (0.2 eq.) heated in 2-propanol (0.3 mL) at 80 °C for 1 h. After cooling to room temperature, the catalyst was then added to a solution of **1a** (0.2 mmol, 1 eq.) and HCO_2H/Et_3N (1.5 : 3, 1.5 eq.) in solvent (1 mL). [b] Isolated yields. [c] Determined by NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC. [e] Reaction run with 0.075 eq. of $[RuCl_2(mesitylene)]_2$ and 0.15 eq. of (*S*,*S*)-DPAE. [f] Reaction run with 0.05 eq. of $[RuCl_2(mesitylene)]_2$ and 0.1 eq. of (*S*,*S*)-DPAE. [g] Reaction run with 0.025 eq. of $[RuCl_2(mesitylene)]_2$ and 0.05 eq. of (*S*,*S*)-DPAE.

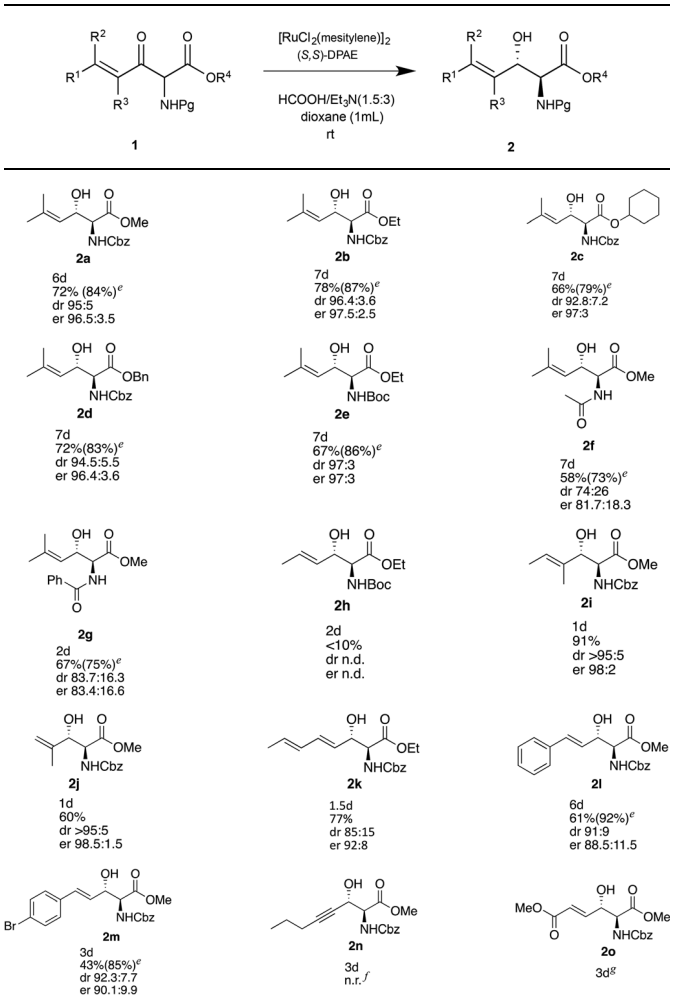
result being obtained with $[RuCl_2(mesitylene)]_2$ (entry 6). Encouraged by this result, other reaction parameters (solvent and catalyst loading) were screened in order to improve the reaction outcome. Performing the reaction in MeOH or CH_3CN did not improve the outcome (entries 8–9), while the use of dioxane or $CHCl_3$ afforded similar results in terms of yields and stereoselectivities as CH_2Cl_2 (entries 8–11). Since the reaction run in dioxane gave the best result this solvent was selected for the final screening of catalyst loading (entries 12–14). It was observed that similar yields but with improved diastereoselectivity could be achieved when lowering the amount of catalyst from 20 mol% to 5 mol%. The best result, 72% yield of **2a** with 95 : 5 dr and 96.5 : 3.5 er, was obtained when using 2.5 mol% of $[RuCl_2(mesitylene)]_2$ and 5 mol% (*S*,*S*)-DPAE (entry 14).

Next the scope of the ATH reaction was investigated by screening a variety of γ-alkenyl-β-keto-α-amido esters **1** and the results are summarized in Table 2. The influence of the ester moiety in the substrate was negligible as compounds **1a–d** all gave the corresponding aminoalcohols **2a–d**, respectively, in good yields and high selectivities. However, the choice of *N*-protecting group influenced the reaction outcome, with *N*-acetyl and *N*-benzoate protected substrates **1f** and **1g** furnishing the corresponding products in lower yields and selectivities compared to **1a**, while *N*-Boc protected **1e** performed equally well as **1a**. The ATH reaction proved to be sensitive to the substitution at the olefin moiety with substrate **1h**, having a disubstituted alkene, giving mostly over-reduced products derived from both 1,4- and 1,2-reductions and only minor amounts of **2h**. Substrate **1i** and **1j**, having a trisubstituted and 1,1-disubstituted olefin moiety, respectively, performed well in the ATH reaction and deliver the corresponding products in good yields, dr and er. Similarly, substrates **1k–m**, having a conjugated olefin moiety, all performed well in the reduction, while alkynyl **1n** was unreactive under these conditions and **1o** gave a complicated mixture of products.

To demonstrate the applicability of the developed methodology it was decided to apply it to the total synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine.[9] Previous syntheses of this natural product has relied on carbohydrate derived strategies and relatively high steps strategies, while the present approach relies on an efficient and non-carbohydrate entry into this class of compounds. Our retrosynthetic analysis is summarized in Scheme 2 and relies on the known cyclization of amino epoxides **10** into (+)-alexine.[10] Compound **10**, in turn is derived from alkene **8**, which can be derived from **2b** using standard transformations (Scheme 2).

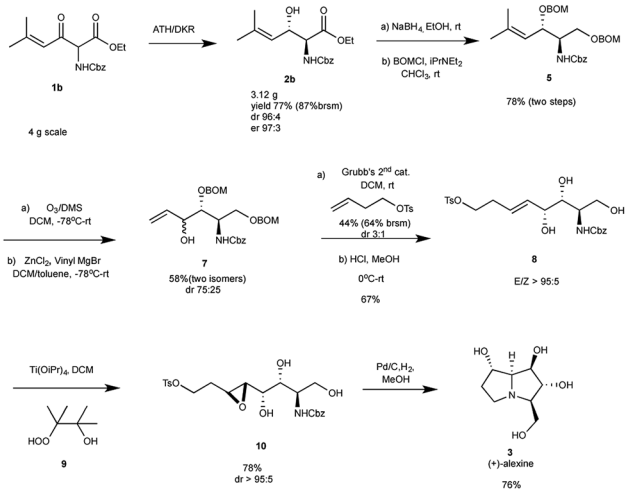
Subjecting ester **1b** (4 g) to the ATH reaction, using the optimized conditions, furnished *anti*-α-amido-β-hydroxy ester **2b** (87% brsm) in high diastereo- and enantioselectivity (*anti*/*syn* 96 : 4, er 97 : 3), which also indicate that the ATH/DKR protocol is scalable. Reduction of **2b** with $NaBH_4$, followed by

Table 2 Exploration of substrates scope[a,b,c,d]



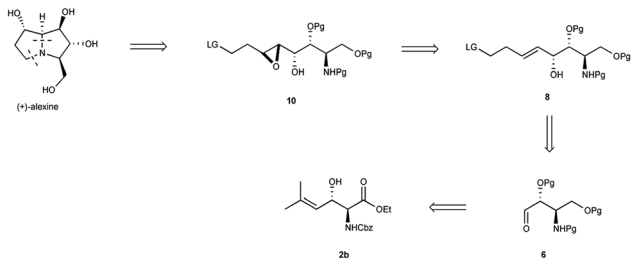
[a] Reaction preformed with $[RuCl_2(mesitylene)]_2$ (0.025 eq.) and (*S*,*S*)-DPAE (0.05 eq.) heated in 2-propanol (0.3 mL) at 80 °C for 1 h. After cooling to room temperature, the catalyst was then added to the β-keto ester **1** (0.2 mmol, 1 eq.) and HCO_2H/EtN_3 (1.5 : 3, 1.5 eq.) in dioxane (1 mL). [b] Isolated yields. [c] dr determined by ^{1}H NMR analysis of the crude reaction mixture. [d] er determined by chiral HPLC. [e] Isolated yields based on recovered start material. [f] No reaction. [g] The reaction gave a complicated mixture of product.

protection of the resulting 1,3-diol as the bis-BOM ether provided **5** (78%, two steps). Ozonolysis of this material followed by a chelation controlled addition of vinylmagnesium bromide afforded compound **7** (58%, dr 75 : 25).[11] Attempts to improve the dr of this step involved screening different solvents, Lewis acids, temperatures and hydroxyl protecting groups, but did not improve the situation.[12] The cross metathesis reaction of mixture **7** with 4-butenol *p*-tolyl-sulfonate in the presence of Grubbs' 2nd generation catalyst provided the *trans* olefin (64% brsm). After the deprotection of benzyloxymethyl group, an undesired diastereomer of compound **8** could be separated by column chromatography, and compound **8** was obtained (67%, dr > 95 : 5) as a pure form. Next the stage was set for the neighbouring group directed epoxidation of **8**, which was accomplished using $Ti(OiPr)_4$ and β-hydroperoxy alcohol **9**, yielding *anti* epoxide **10** (78%) as the only detectable isomer.[13] Deprotection of **10** (Pd/C, H_2, MeOH) followed by purification on silica gel afforded (+)-alexine (**3**) in 76% yield as a white solid. The ^{1}H-NMR, ^{13}C-NMR data, melting point and the optical rotation (mp 160–162 °C, $[\alpha]_D^{20} = +42.1$ (c 0.3H_2O)) were in good agreement with the published data for (+)-alexine[9] (mp 162–163 °C, $[\alpha]_D^{20} = +40$ (c 0.25 in H_2O)) (Scheme 3).



Scheme 3 Total synthesis of (+)-alexine.

In summary, we have developed an operationally straightforward synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters from the corresponding racemic α-amino-β-keto esters by using a ATH/DKR protocol. This method gives moderate to excellent yields, diastereoselective and enantioselectivities for a broad range of substrates. In order to highlight the versatility of the methodology it was applied in an asymmetric synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine (**3**, 8 steps and 11.5% overall yield from **2b**).



Scheme 2 Retrosynthetic analysis of (+)-alexine.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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