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A highly enantioselective synthesis of cyclic α-amino acids involving a one-pot, single catalyst, tandem hydrogenation–hydroformylation sequence†

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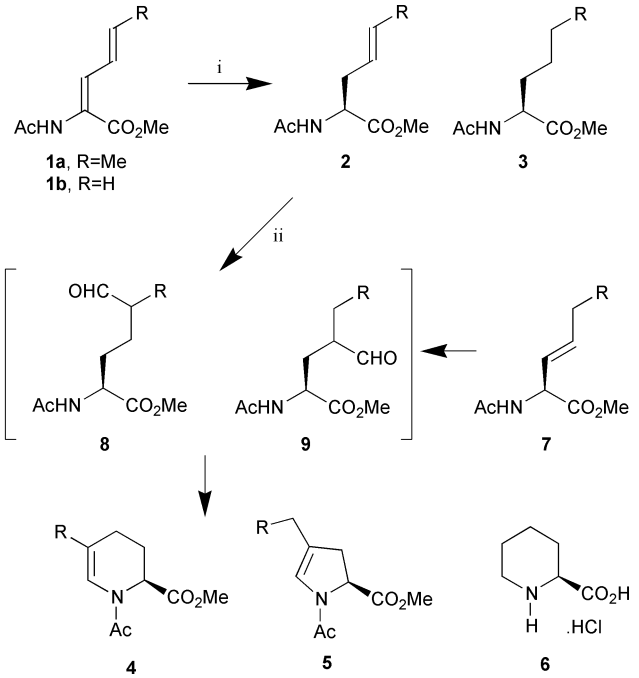
Tandem enantioselective hydrogenation followed by a hydroformylation–cyclisation sequence leading to cyclic α-amino acids with ee's > 95% can be achieved in a single pot, one catalyst system by successive reactions of prochiral dienamide esters with H_2 followed by H_2/CO using Rh(I)-DuPHOS.

Cyclic amino acids are of increasing biological importance because of their relationship to naturally occurring biological molecules, *e.g.* the izidine alkaloids[1] (piperidines), kainic acid analogues[2] (pyrrolidines), and their use in peptidomimetics.[3] Recent syntheses of pipecolic acid derivatives have involved aldol condensation–reductive amination of aspartate β-aldehyde,[4] intramolecular cyclohydrocarbonylation of unsaturated amides[5] and ruthenium catalysed ring closing metathesis.[6] Both of these latter preparations start with allylglycine which is available in both enantiomeric forms.[7] In spite of these recent advances, there appears to be a demand for facile routes to this class of compound as other general syntheses are relatively limited in scope. In this communication we describe a general synthesis of either enantiomer of piperidino- and pyrrolidino-based α-amino acids by a sequence which, in its final form, involves a single pot, one catalyst reaction sequence. Such tandem sequences are becoming increasingly important in organic synthesis and have recently been used for isomerisation–carbonylation of alkenes.[8] Domino reactions employing hydroformylation–condensation–hydrogenation sequences have also recently been reported.[9]

Rhodium catalysed hydrogenation of the prochiral dienamide ester **1a** under conditions reported by Burk[10] gave the allylglycine derivative **2a** in high enantiomeric excess (> 95%) and yield (98%) (Scheme 1). Either enantiomer of **2a** could be obtained by the use of (*R*,*R*)- or (*S*,*S*)-Et-DuPHOS with the (*R*,*R*)-catalyst giving the (*R*)-enantiomer of **2a**.[10,11] Excellent regioselectivity was observed with < 5% of the saturated product **3a** being produced. The unsubstituted analogue **1b** was also hydrogenated under milder conditions to give **2b** with excellent regioselectivity but with a slightly increased amount of over-reduced material **3b** (5–15%). The enantioselectivity was again > 95% as shown by chiral gas chromatography (Scheme 1).

Ojima and co-workers have previously reported preparation of pipecolic acid derivatives from protected allylglycines closely related to **2b**.[5] Reactions of **2b** using rhodium–phosphine catalysts with H_2/CO under conditions previously used in our work[12] gave very good isolated yields (*ca.* 70%) of the cyclic amino acid derivatives **4b** and **5b** (Table 1, entries 1 and 2) (Scheme 1). The compounds were readily separated and chiral hplc showed that the enantiomeric excess had not been compromised. Confirmation that the (*R*)-configuration was present in samples of **4b** prepared using (*R*,*R*)-Et-DuPHOS was obtained by conversion of **4b** to (*R*)-pipecolic acid hydrochloride **6** and comparison of optical rotation values.[13]

The isolated piperidine **4**:pyrrolidine **5** ratio originates from the regioselectivity exhibited during hydroformylation. The observed selectivity (< 2:1 for **4b**:**5b**), however, was considerably lower than expected given that hydroformylation of a terminal alkene using PPh_3 as ligand would be expected to yield a piperidine:pyrrolidine ratio of *ca.* 2:1, whereas the bulkier BIPHEPHOS ligand should bias this ratio to *ca.* 9:1.[12,14] An



Scheme 1 (i) **1a**: (*S*,*S*)-Et-DuPHOS-Rh(I), H_2 (90 psi), 2 h, PhH, rt; **1b**: (*S*,*S*)-Et-DuPHOS-Rh(I), H_2 (30 psi), 3 h, PhH, rt. (ii) H_2/CO (1:1), 80–400 psi, 80–100 °C, 20–72 h. $[Rh(OAc)_2]_2$, PPh_3 or BIPHEPHOS with substrate:Rh(I):phosphine ratio of 100:1:2.

Table 1 Rhodium catalysed hydroformylation of chiral enamides **2a** (R = Me) and **2b** (R = H)[a]

Entry	R	Catalyst System[b]	H_2/CO (psi)	T (°C)	Time (h)	Product Ratio (**4**:**5**)	Yield (%)[c]	% ee (**4**/**5**)[g]
1	H	A	400	80	72	50:50	73	--/87
2	H	B	400	80	20	63:37	66	88/--
3	H	B	100	80	20	71:29	54[d]	--/87
4	H	B	80	80	20	78:22	—[e]	
5	H	B	80	80	72	66:34	75	99/--
6	Me	A	400	80	20	67:33	45	91/98
7	Me	B	400	80	20	100:0	37[f]	
8	Me	B	400	100	72	91:9	81	97/--

[a] Reaction conditions: Substrate (0.3 mmol) : $[Rh(OAc)_2]_2$: PPh_3 or BIPHEPHOS ratio = 100:1:2 in benzene (5–10 ml) with H_2/CO (1:1). [b] Catalyst code: A = Rh-PPh_3, B = Rh-BIPHEPHOS. [c] Isolated yield of cyclic products **4** and **5** after chromatography. [d] Crude product contained *ca.* 20% isomerised alkenamide **7**. [e] Crude product contained *ca.* 50% isomerised alkenamide **7**. [f] Aldehydes **8a** and **9a** (*ca.* 1:1) also obtained. [g] -- Signifies that enantioselectivity was not assessed.

† Electronic supplementary information (ESI) available: experimental information. See http://www.rsc.org/suppdata/cc/b2/b200374k/

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explanation for this anomaly became apparent after conducting the hydroformylation experiments under milder conditions. Reaction of **2b** at 80 °C with 100 psi of H_2/CO over 20 h (entry 3) gave a modest yield (54%) of **4b** and **5b** and *ca*. 20% of the isomerised alkenamide **7**. Significantly, Rh(I)-BIPHEPHOS catalysed hydroformylation of **7** would favour reaction remote from the bulky amino acid moiety resulting in pyrrolidine **5b** after cyclisation and dehydration (Scheme 1). This secondary route to **5b** explains the higher than expected amounts of pyrrolidine in reactions involving **2b**. Under lower hydroformylation pressure (80 psi) an even greater percentage of **7** (*ca*. 50%) was observed after 20 h (entry 4) and extended reaction over 72 h gave significant amounts of **5b** (entry 5).

Hydroformylation of the homologue **2a** at 80 °C with 400 psi H_2/CO using PPh_3 as ligand gave **4a** and **5a** in a 2 : 1 ratio (entry 6) whilst a similar reaction using BIPHEPHOS gave a significant amount of the uncyclised aldehydes **8a** and **9a** together with piperidine **4a** (entry 7). Increasing the temperature and reaction time led to complete conversion and isolation of cyclic compounds **4a** and **5a** in high yield and in a ratio of 9 : 1.

A tandem reaction was then investigated which capitalized on the disparate operating conditions of the two Rh-DuPHOS and Rh-BIPHEPHOS catalysts. Under mild reaction pressures, only the Rh-DuPHOS catalyst would be expected to facilitate hydrogenation of the enamide substrates **1** ensuring the maintenance of high enantioselectivity. Hence, in the presence of *both* Rh-DuPHOS and Rh-BIPHEPHOS, hydrogenation of **1b** (rt, 30 psi of H_2, 3 h) followed by hydroformylation (80 °C, 80 psi of H_2/CO) gave **4b** and **5b** in a 2 : 1 ratio and 63% isolated yield. Importantly, the enantiomeric excess of **4b** and **5b** was found to be >95% (entry 9, Table 2). A similar reaction sequence involving **1a** with Rh-DuPHOS and Rh-PPh_3 gave **4a** and **5a** in *ca*. 1 : 1 ratio in 81% isolated yield (entry 10). The ee of **4a** and **5a** were also shown to be ≥ 95% by chiral hplc.

Next we investigated whether a single catalyst, namely Rh(I)-DuPHOS, could be employed to facilitate both hydrogenation and hydroformylation. To our knowledge, the use of Rh-DuPHOS as a hydroformylation catalyst has not been previously reported. Reaction of dienamide **1b** in the presence of Rh-DuPHOS alone, initially with H_2 at ambient temperature and then with H_2/CO (80 psi) at 80 °C, gave a product containing significant amounts of the isomerised alkene **7** (entry 11). Reaction using a higher pressure of H_2/CO (400 psi) gave complete conversion to **4b** and **5b** in *ca*. equimolar ratio in 91% isolated yield with excellent enantioselectivity (entry 12). It appears that the Rh-DuPHOS system is slightly less efficient for hydroformylation than the Rh-BIPHEPHOS system (compare entries 5 and 11). A similar diminution in rate was observed for a reaction of **1a** in the presence of Rh-DuPHOS where hydroformylation under conditions giving complete conversion using Rh-PPh_3 (entry 6, Table 1; entry 10, Table 2) gave substantial amounts of aldehydes (**8a** and **9a**) (entry 13). A reaction under more forcing conditions gave complete conversion to the piperidine **4a** which was isolated as the sole product in 58% yield and with 96% ee (entry 14).

These results clearly establish that it is possible to obtain cyclic α-amino acids in good to very good yields and with excellent enantioselectivity using a single catalyst in a single pot *via* a tandem reaction sequence.

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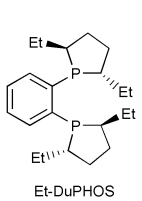
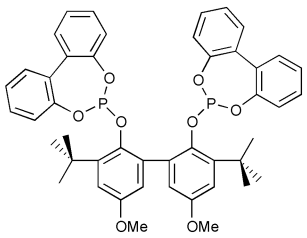
Table 2 Rhodium catalysed tandem hydrogenation and hydroformylation of dienamides **1a** (R = Me) and **1b** (R (R = H)[a]

Entry	R	Catalyst System[b]	H_2/CO (psi)	*T* (°C)	Time (h)	Product Ratio (**4** : **5**)	Yield (%)[c]	% ee (**4**/**5**)
9	H	B + C	80	80	72	67 : 33	63	95/95
10	Me	A + C	400	80	20	56 : 44	81	95/99
11	H	C	80	80	72	74 : 26	—[d]	
12	H	C	400	80	72	54 : 46	91	95/99
13	Me	C	400	80	20	83 : 17	35[e]	99/99
14	Me	C	800	150	72	100 : 0	58	96/—[f]



Et-DuPHOS



BIPHEPHOS

[a] Reaction conditions: Substrate (0.3 mmol) : Rh-Et-DuPHOS : Rh[$(OAc)_2$]$_2$: PPh_3 or BIPHEPHOS ratio = 100 : 1 : 1 : 2 in benzene (5–10 ml) with H_2 (30 psi, 3 h for **1b** and 90 psi, 2 h for **1a**) at ambient temperature followed by H_2/CO (1 : 1). [b] Catalyst code: A = Rh-PPh_3, B = Rh-BIPHEPHOS, C = Rh-Et-DuPHOS. [c] Isolated yield of cyclic products **4** and **5** after chromatography. [d] Crude product contained *ca* 40% isomerised alkenamide **7**. [e] Aldehydes **8a** and **9a** also obtained. [f] Enantioselectivity was not assessed.

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