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# Asymmetric $\alpha$ -Arylation of Amino Acids

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## Summary

Quaternary amino acids, in which the  $\alpha$ -carbon bearing the amino and carboxyl groups also carries two carbon substituents, have an important role as modifiers of peptide conformation and bioactivity and as precursors of medicinally important compounds.<sup>1,2</sup> In contrast to enantioselective alkylation at this  $\alpha$ -carbon, for which there are several methods,<sup>3-8</sup> general enantioselective introduction of an aryl substituent at the  $\alpha$ -carbon is synthetically challenging.<sup>9</sup> Nonetheless, the product  $\alpha$ -aryl amino acids and their derivatives have proved valuable as precursors to bioactive molecules.<sup>10,11</sup> Here we describe the synthesis of quaternary  $\alpha$ -aryl amino acids from enantiopure amino acid precursors by  $\alpha$ -arylation without loss of stereochemical integrity. Our approach relies on the temporary formation of a second stereogenic centre in an *N'*-arylurea adduct<sup>12</sup> of an imidazolidinone derivative<sup>6</sup> of the precursor amino acid, and uses readily available enantiopure amino acids both as a precursor and as a source of asymmetry. It avoids the use of high-value transition metals, and allows arylation with electron-rich, electron-poor, and heterocyclic substituents. Either enantiomer of the product may be formed from a single amino acid precursor. The method is practical and scalable, providing the opportunity to produce  $\alpha$ -arylated quaternary amino acids in multi-gram quantities.

Among the most practical and commonly used methods<sup>13,14</sup> for the synthesis of  $\alpha$ -alkylated amino acids are those developed by Seebach *et al.* that employ readily available chiral amino acids both as starting material and as source of chirality, using the 'self-regeneration of stereocentres'.<sup>6</sup> This strategy relies on diastereoselective formation of an imidazolidinone or oxazolidinone to create a new stereogenic centre whose configuration survives the formation of a planar amino acid enolate, and directs its alkylation to form a quaternary stereocentre with control over absolute configuration.

The mechanistically unusual<sup>15</sup> N to C aryl migration that takes place in anionic derivatives of ureas was first reported for the construction of stereodefined quaternary centres from configurationally stable organolithiums,<sup>12</sup> and it has been used to provide racemic 5,5-disubstituted hydantoin.<sup>16</sup> Stereoselective versions of this hydantoin synthesis employing conformational chiral memory<sup>17</sup> or a stoichiometric auxiliary<sup>18</sup> suggested that a practical stereoselective version of this intramolecular arylation based on Seebach's imidazolidinone alkylation chemistry might offer a strategy for the synthesis of unavailable enantiopure  $\alpha$ -arylated amino acids (Fig. 1).

We therefore explored *N'*-aryl ureas as a potential intramolecular source of the coupling partner for a corresponding arylation reaction. A versatile synthesis of the *N*-carbamoylimidazolidinones **3** was required, and our initial synthetic approach is shown in Figure 2a. Treatment of L-AlaNHMe with pivaldehyde and trifluoroacetic acid gave good selectivity for the *trans* diastereoisomer of the imidazolidinone's trifluoroacetate salt.<sup>19</sup> *In situ* chloroformylation with triphosgene in base gave high yields of the *N*-chloroformylimidazolidinones **1-Ala** as a 4:1 mixture of *trans* and *cis* diastereoisomers *trans*-**1-Ala** and *cis*-**1-Ala**. These were readily separated by column chromatography and their relative configurations were established by X-ray crystallography (Figure 2b) and NOE experiments (see Supplementary Information).

The minor diastereoisomer *cis*-**1-Ala** acylated *N*-methylaniline (PhNHMe) cleanly in refluxing dichloromethane to give the urea *cis*-**3-Ala-a** in high yield (Figure 2a, and Table 1, entry 1). The major *trans* diastereoisomer of **1-Ala** (which characteristically and diagnostically exhibited slow N–CO rotation by NMR: see Supplementary Information) was much less reactive. The urea *trans*-**3-Ala-a** was formed only when *trans*-**1-Ala** was activated with potassium iodide,<sup>20</sup> and a reaction time of 45 h in refluxing CH<sub>2</sub>Cl<sub>2</sub> was required for acceptable yields (Figure 2a and Table 1, entries 2-4).

We were now in a position to address the question of the key C–C bond forming step: would ureas **3-Ala** undergo the rearrangement we had discovered with other amino acid enolates to provide a means of arylating the amino acid  $\alpha$ -centre in a diastereoselective manner? *Cis*- and *trans*-**3-Ala-a** were each cooled and treated with base to form an enolate, which was allowed to warm to room temperature. Initial experiments with LDA showed that enolate formation was complete at –78 °C, (Table 2, entry 1) and that warming to room temperature was sufficient to induce 1,4 migration of the phenyl ring to the enolate carbon yielding the C-arylated product imidazolidinone **4-Ala-a** from *trans*-**3** and its enantiomer *ent*-**4-Ala-a** from *cis*-**3** (entries 2, 3). The best yields were obtained on forming the enolate at 0 °C, and even with the milder base KHMDS **4-Ala-a** was formed in 95% yield from *trans*-**3-Ala** as a single diastereoisomer on a >1 g scale (Table 2, entry 4). These conditions (shown as 'Method A' in Figure 2a) were identified as optimal, and a similar yield of the enantiomeric product *ent*-**4-Ala** was obtained under these conditions from *cis*-**3-Ala** (Table 2, entry 5). In neither case was any trace of the other diastereoisomer of **4-Ala**

detectable in the product by  $^1\text{H}$  NMR, and HPLC on a chiral stationary phase indicated that the product was essentially enantiomerically pure (>99:1 *er*).

Either enantiomer of the product **4-Ala** was formed from the same L-Ala starting material, simply by choice of route. However, some work on the synthesis of **3** was still needed for this to become a general method for arylating amino acids other than alanine. Two problems remained: firstly, although *cis*-**3-Phe** was successfully formed from *cis*-**1** in the presence of KI (Table 1, entry 5), *cis*-**1** was only available in low yield as it is formed as the minor diastereoisomer in the preceding chloroformylation step. Secondly, the unreactivity of the major diastereoisomer *trans*-**1** meant that *trans*-**3** could not be formed reliably by this route from amino acids other than Ala: attempted acylations using *trans*-**1-Phe** were unproductive even using KI as an activator (Table 1, entry 6).

A more robust synthesis of *trans*-**4** was provided by returning to the easily formed *N*-chloroformylimidazolidinones *trans*-**1** as alternative precursors. Although acylation of a neutral *N*-methylaniline with *trans*-**1** had proved insufficiently general as a way of making **3** (Table 1, entry 6), reaction of *trans*-**1-Ala**, *trans*-**Phe** or *trans*-**Leu** with the anions of a range of *N*-methyl anilines, formed using an excess of KHMDS, not only promoted the acylation of the amine to give *trans*-**3** but also led to deprotonation and rearrangement of **3** to give **4**. Optimised conditions for this one-pot procedure (labelled Method B in Figure 2a) involved two separate additions of KHMDS. Method B provided an efficient synthesis of an array of products **4-Ala**, **4-Phe** and **4-Leu** bearing a representative selection of substituted aryl rings in high yield and high diastereoselectivity (see Supplementary Information).

To explore a similarly efficient route to *ent*-**4** from the same L-amino acids, we turned to an alternative synthesis of *cis*-**3** with complementary diastereoselectivity. Seebach showed that while *trans* imidazolidinones are formed at lower temperatures under acidic conditions, diastereoselectivity towards *cis* *N*-acylimidazolidinones can be achieved by acylation of the pivaldimine derivatives of amino acids, probably because of the *cis*-selectivity exhibited by cyclisation of the hindered, planar *N*-acyliminium intermediate.<sup>21</sup> We found that urea *cis*-**3-Ala** was indeed formed when the imine **2-Ala** was acylated with *N*-methyl-*N*-phenylcarbamoyl chloride (Figure 2a, and Table 1, entries 7, 8). Optimal yields of the pure *cis* diastereoisomer were obtained in refluxing toluene or dichloroethane in the presence of 5 mol% DMAP (entries 10, 11), but with stoichiometric Et<sub>3</sub>N no product was obtained (entry 9). We assume that under these conditions of nucleophilic catalysis, cyclisation to the imidazolidinone is reversible, with the rather unreactive carbamoyl chloride selectively acylating the less hindered *cis* diastereoisomer. The method was successfully used to form *cis*-*N*-carbamoylimidazolidinones *cis*-**3-Ala**, *cis*-**3-Phe**, and *cis*-**3-Leu** bearing substituted aryl rings by way of their imines **2** (see Supplementary Information). These imidazolidinone substrates were subjected to the conditions (Method A) previously optimised for *cis*- and *trans*-**3-Ala** to yield the products *ent*-**4** enantiomeric with those formed from *trans*-**3**.

The 'S-selective' and 'R-selective' routes highlighted in red in Figure 2a thus provide enantiocomplementary routes to the imidazolidinones **4** and *ent*-**4** from the representative L-amino acids L-Ala, L-Phe and L-Leu. These structures are simple derivatives of quaternary amino acids, and were converted into the target  $\alpha$ -arylated amino acids **5** by hydrolysis under acid conditions. Excellent yields of the enantiopure amino acids **5** were obtained by *N*-methylation of the urea function of **4** followed by microwave heating with 6 M HCl (Figure 2a, Method D and Figure 2d). The *p*-cyano function of **4-Ala-b** and **4-Leu-b** was hydrolysed under these conditions to give the

carboxylated phenylglycine derivatives **5-Ala-b'** and **5-Leu-b'**. **5-Ala-b'** is the mGluR antagonist (S)-M4CPG.<sup>10</sup>

Hydrolysis without preliminary *N*-methylation led to competitive formation of the corresponding *N*-methylhydantoins **6** in moderate yield (Figure 2c) owing to cyclisation of the urea onto the newly revealed carboxylic acid. These hydantoins **6** could be hydrolysed cleanly to **5** in a second step, but are nonetheless themselves valuable target structures.<sup>2</sup> A more versatile synthesis of **6** was provided by treatment of the methyl ester **8-Phe-e-OMe** with *tert*-butyl isocyanate to give **6-Phe-e**, the *tert*-butyl group being removable to give **6-Phe-e'** under acid conditions (Figure 2e).

Other products of value for the use of arylated amino acids in synthetic procedures such as peptide formation were also formed from **5** or directly from **4** (Figure 2e). Protection of the amino or carboxyl group under the conditions shown in Figure 4 made available the Cbz, Boc or Fmoc protected carbamates **7** and the esters **8**. Despite the steric hindrance of the quaternary amino acid, dipeptide **9** was formed cleanly on coupling **Cbz-7-Ala-d** to L-Phe-OEt under standard conditions.

Having shown that the base-promoted rearrangement of **3** provides a viable method for the arylation of an initial selection of amino acids, we returned to the synthesis of **4** and *ent*-**4** with the aim of extending its scope to other amino acids, and exploring the scope of migrating aryl groups tolerated by the method. The optimal conditions of the 'S-selective route' and the 'R-selective route' were applied to a range of amino acid derived starting materials, and the successful outcomes of these reactions are summarised in Figure 3.

Halogenated (**c-g**) rings, even those bearing bromo substituents, rearranged without evidence of dehalogenation or benzyne formation. Sterically hindered *ortho*-substituted (**i**) and 1-naphthyl rings (**h**) also rearranged in good yield. Despite the fact that the rearrangement is formally an intramolecular nucleophilic aromatic substitution reaction, it shows remarkable tolerance to variations in the aryl migrating group, with conjugated (**h**), electron-deficient (**b**) and electron rich (**i-l**) rings all taking part in the reaction. All three orientations of a pyridyl ring (**m-o**) gave rearranged products regiospecifically.

Beyond Ala, Phe and Leu, the functionalised side chains of Met, Tyr and Trp were tolerated, with arylation of Tyr being successful even without protection of its hydroxyl group. Phenylglycine (Phg) was also arylated, allowing the enantioselective synthesis of chiral diaryl glycine derivatives **4-Phg** (including the enantioselectively deuterated **4-Phg-p**). With Phg, it was necessary to use Method B (starting from *trans*-**1-Phg**) to ensure high enantiomeric ratios, as its acidifying sidechain evidently leads to some racemisation in the synthesis of *cis*-**3-Phg** via imine **2-Phg**. Arylation of the highly hindered valine-derived **3-Val** failed with KHMDS, but rearrangement of **3-Val-a** to **4-Val-a** proceeded in excellent yield with a more powerful, less bulky base, lithium diethylamide. A slight loss in diastereoselectivity was seen in this reaction possibly due to the more demanding steric requirements of a transition state carrying both *t*-Bu and *i*-Pr *cis* on the imidazolidinone ring.

The mechanism by which the enolate of **3** forms **4** is intriguing. Formally an intramolecular nucleophilic aromatic substitution (S<sub>N</sub>Ar), the reaction bears some similarity with the Smiles and Truce-Smiles rearrangements,<sup>22,23</sup> but is distinguished from almost all known examples of these rearrangements by the lack of requirement for an electron-deficient migrating ring. Sensitivity to electronic features may be measured by the Hammett reaction constant  $\rho$ , and we explored the kinetics of the reaction by *in situ* infra-red (IR) spectroscopy in order to estimate a value of  $\rho$  for the rearrangement.

Preliminary IR studies using *cis*-**3-Ala-a** under the optimised conditions for the reaction (1.5 equiv. KHMDS in THF at room temperature) revealed no reaction intermediates, indicating that rearrangement was faster than enolate formation at room temperature. Changing the base to LDA and carrying out the rearrangement at  $-20\text{ }^{\circ}\text{C}$  decreased the rate of both deprotonation and rearrangement, and revealed an intermediate on the reaction pathway (Figure 4a, 4b). This intermediate was identified as the enolate **E** (Figure 4a) by noting that it had no C=O stretching absorption corresponding to an amide carbonyl group ( $1710\text{ cm}^{-1}$  in *cis*-**3-Ala-a**) but retains the urea ( $1630\text{ cm}^{-1}$ ) and aromatic bands at  $1500\text{--}1600\text{ cm}^{-1}$ . The rate of decay of this intermediate was identical for both *cis*-**3-Ala-a** and *trans*-**3-Ala-a**, confirming that it is a common intermediate from both diastereoisomers, and treating the isolated product with LDA gave an IR spectrum identical with that of the species present at the end of the reaction, identifying it as the product anion **P** (Figure 4a). Confirmation that the reaction is intramolecular was provided by a cross-over experiment in which *cis*-**3-Ala-b** was mixed with *cis*-**3-Met-c** (both of which rearrange at comparable rates) and treated with KHMDS. A mass spectrum of the crude reaction mixture showed molecular ions corresponding only to **4-Ala-b** and **4-Met-c**.

A Hammett plot was constructed by treating a series of imidazolidinones **3-Ala** bearing a selection of aryl substituents with an excess (5 equiv.) of LDA at  $-20\text{ }^{\circ}\text{C}$ , and the formation of product anion **P** monitored using its characteristic IR bands at ca.  $1690$  and  $1630\text{ cm}^{-1}$ . Under these conditions, the formation of the product from the enolate followed first-order kinetics, and the linear section of a plot of  $\ln([\mathbf{P}]_{\infty} - [\mathbf{P}])$  vs.  $t$  gave a rate constant  $k_{\text{obs}}$  for each substrate (Fig. 4c). A Hammett plot of  $\log k_{\text{obs}}$  vs  $\sigma^{-}$  is shown in Fig 4d: the plot shows a downwards bend characteristic of a change in rate-determining step, with enolate formation being rate-limiting for electron-deficient rings (no enolate was detectable by IR during the rearrangement of **3-Ala-b** or **3-Ala-c**). For the electron-rich domain of the plot, the value of  $\rho$  is  $+4.5$ , consistent with substantial build-up of negative charge on the migrating ring during the reaction. This  $\rho$  value is nonetheless smaller in magnitude than those of 'classical' intermolecular  $\text{S}_{\text{N}}\text{Ar}$  reactions,<sup>24,25</sup> possibly indicating that the reaction proceeds without the intermediacy of an anionic 'Meisenheimer complex'.<sup>26-28</sup> Electron-rich substitution patterns are unreactive in such intermolecular substitutions, and we assume that in our system the conformational restriction imposed by the urea linkage<sup>29</sup> must enforce attack of the enolate on the ring, irrespective of the ring's inability to stabilise a negative charge.<sup>30</sup>

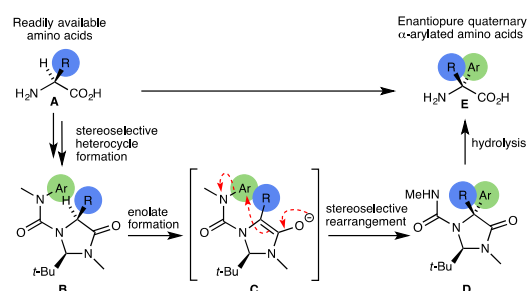
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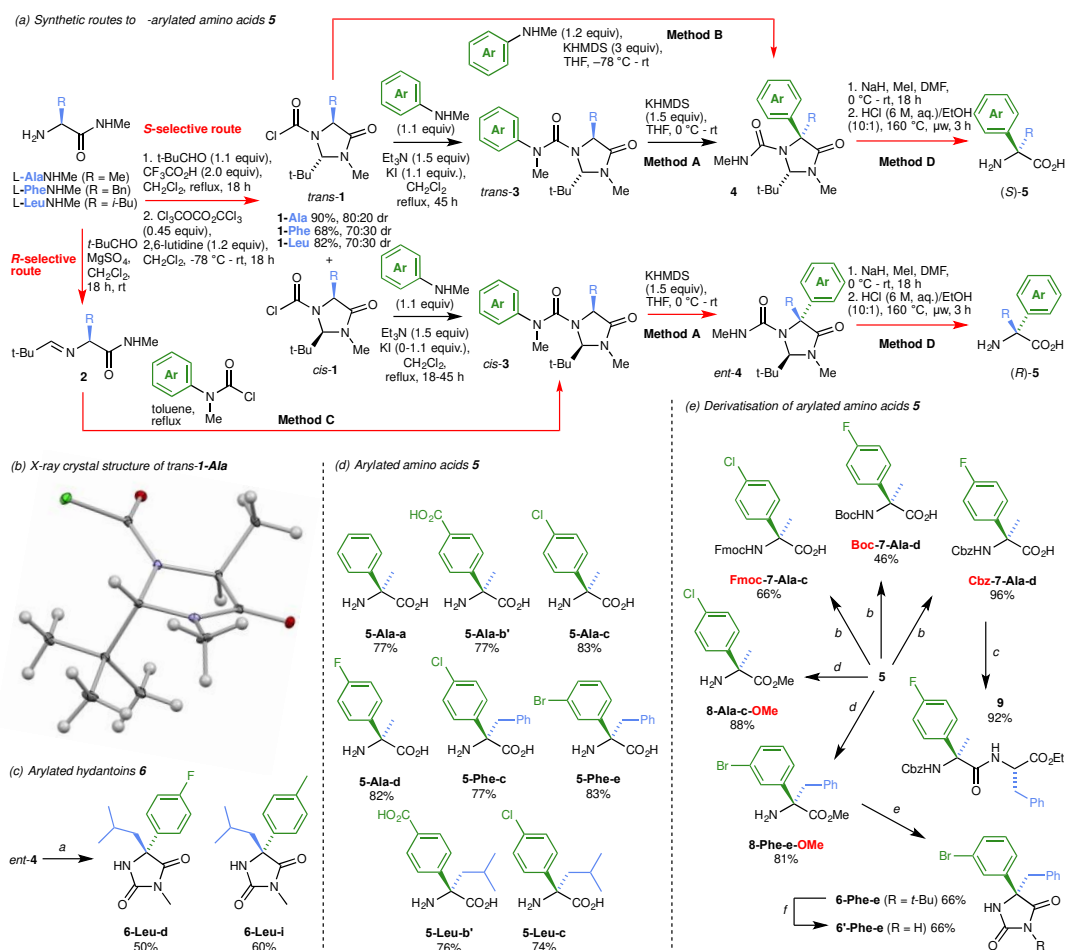
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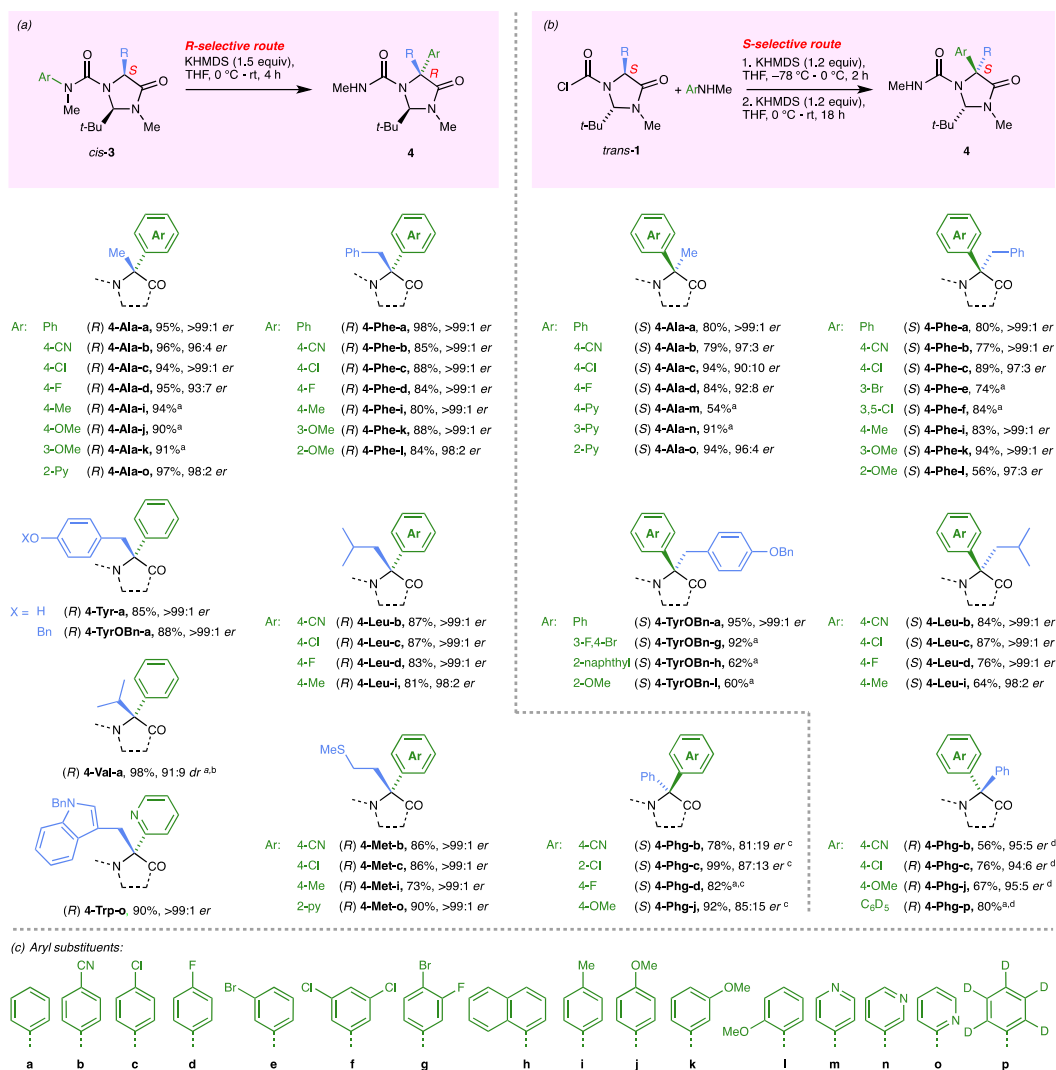




**Figure 1: Stereoselective arylation of amino acids.** Our strategy for stereoselective arylation of amino acids by way of imidazolidinyl ureas. An amino acid **A** is converted diastereoselectively into an imidazolidinone **B** carrying a pendent urea function. Treatment with base forms an enolate **C** in which the urea's aromatic substituent Ar migrates to the rear face of the imidazolidone, directed by the bulky *tert*-butyl group, as indicated by the red dotted arrows. Hydrolysis of the product **D** reveals the quaternary α-aryl amino acid **E**.

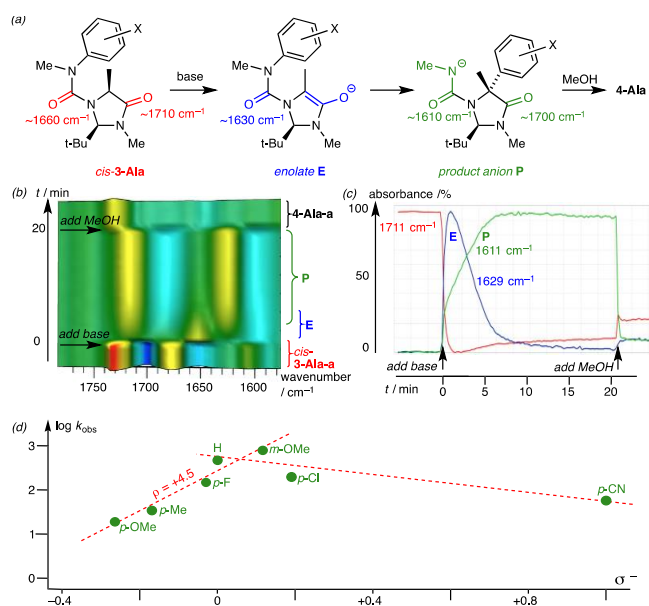


**Figure 2. Arylation of amino acids by way of imidazolidinone ureas.** (a) Synthetic pathways from L-amino acids to quaternary  $\alpha$ -arylated amino acids **5** by way of *N*-chloroformylimidazolidinones **1** or imines **2**, *N'*-aryl imidazolinyl ureas **3**, and C-aryl imidazolidinones **4**. The sequence of method B and method D shown by the red arrow starting from **1** constitutes an 'S-selective route' to **5** from an L-amino acid, while the sequence of methods C, A and D shown by the red arrows from **2** constitutes an 'R-selective route' from an L-amino acid. (b) The stereochemistry of **trans-1-Ala** confirmed by X-ray crystallography. (c) Representative  $\alpha$ -arylated hydantoins formed by hydrolysis of *ent i*-**4**. (d) Yields of representative  $\alpha$ -arylated amino acids **5** formed by methylation and hydrolysis of **4**. (e) Derivatisation of representative quaternary  $\alpha$ -arylated amino acids **5** by N-protection, peptide coupling, esterification or hydantoin formation. *Conditions:* *a* 1. HCl (6 M, aq.), 130 °C (sealed tube), 18 h; *b* 1. *N*-Methyl-*N*-(trimethylsilyl) trifluoroacetamide, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 4 h; 2. CbzOSu or Boc<sub>2</sub>O or FmocOSu, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; 3. MeOH, rt, 15 min; *c* 1. K-Oxyma, EDC.HCl, *i*-Pr<sub>2</sub>NEt, DMF, 0 °C-rt, 15 min; 2. L-Phe-OEt.HCl, DIPEA, 72 h; *d* Me<sub>3</sub>SiCHN<sub>2</sub>, benzene/MeOH (4:1), rt, 18 h; *e* 1. *t*-BuNCO, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 18 h; 2. *t*-BuOK, THF, rt, 18 h; *f* HBr, AcOH (1:1), 120 °C, 18 h.



**Figure 3. Scope of the imidazolidinone arylation: amino acids and migrating groups.** (a) Product structures, yields and *er* from use of the optimised R-selective route via L-amino-acid derived imidazolidinones cis-3. 'Ar' indicates either the aryl substituent itself or the substituent(s) on a phenyl ring. (b) Product structures, yields and *er* from use of the optimised S-selective route via L-amino-acid derived imidazolidinones trans-1. (c) Structures of the aryl substituents introduced by these methods.

Footnotes: <sup>a</sup>*er* not determined; <sup>b</sup>LiNEt<sub>2</sub> used instead of KHMDS (which gave no product). The product **4-Val-a** contained some of the epimeric imidazolidinone as a result of incompletely diastereoselective rearrangement. <sup>c</sup>D-Phenylglycine was used as starting material, so product has *S* absolute configuration. <sup>d</sup>D-Phenylglycine was used as starting material, so product has *R* absolute configuration.



**Figure 4. Mechanism of the rearrangement.** (a) Proposed reaction pathway, with approximate C=O stretching frequencies; (b) *In situ* IR trace (first-derivative plot) of the reaction of *cis*-3-Ala-a showing diagnostic changes in carbonyl stretching frequencies; (c) plot of absorbance against time for peaks at 1711 cm<sup>-1</sup> (red, starting material), 1629 cm<sup>-1</sup> (blue, enolate **E**), 1611 cm<sup>-1</sup> (green, product anion **P**); (d) Hammett plot of log  $k_{obs}$  vs.  $\sigma^-$ , consistent with rate-determining rearrangement for electron-rich rings and rate-determining deprotonation for electron-deficient rings. The gradient of the electron-rich domain to the left of the plot,  $\rho = +4.5$  is consistent with substantial charge build up on the aryl substituent during the rearrangement.

**Table 1: Optimising the synthesis of **3****  
 Extended Data Table 1: Optimising the synthesis of **3**

entry	starting materials	solvent*	base <sup>†</sup>	additive	product	yield
1	<i>cis</i> - <b>1-Ala</b> + PhNHMe	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	—	<i>cis</i> - <b>3-Ala-a</b>	95
2	<i>trans</i> - <b>1-Ala</b> + PhNHMe	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	—	—	0
3	<i>trans</i> - <b>1-Ala</b> + PhNHMe	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	KI <sup>‡</sup>	<i>trans</i> - <b>3-Ala-a</b>	40
4	<i>trans</i> - <b>1-Ala</b> + PhNHMe	CH <sub>2</sub> Cl <sub>2</sub> <sup>§</sup>	Et <sub>3</sub> N	KI <sup>‡</sup>	<i>trans</i> - <b>3-Ala-a</b>	86
5	<i>cis</i> - <b>1-Phe</b> + PhNHMe	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	KI <sup>‡</sup>	<i>cis</i> - <b>3-Phe-a</b>	90
6	<i>trans</i> - <b>1-Phe</b> + PhNHMe	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	KI <sup>‡</sup>	<i>trans</i> - <b>3-Phe-a</b>	20
7	<b>2-Ala</b> + PhMeNCOCI	MeCN	—	—	<i>cis</i> - <b>3-Ala-a</b>	50
8	<b>2-Ala</b> + PhMeNCOCI	PhMe	—	—	<i>cis</i> - <b>3-Ala-a</b>	65
9	<b>2-Ala</b> + PhMeNCOCI	PhMe	Et <sub>3</sub> N	—	<i>cis</i> - <b>3-Ala-a</b>	<5
10 <sup>  </sup>	<b>2-Ala</b> + PhMeNCOCI	PhMe	—	DMAP <sup>¶</sup>	<i>cis</i> - <b>3-Ala-a</b>	88
11	<b>2-Ala</b> + PhMeNCOCI	(CH <sub>2</sub> Cl <sub>2</sub> ) <sub>2</sub>	—	DMAP <sup>¶</sup>	<i>cis</i> - <b>3-Ala-a</b>	85

\*Reaction carried out at reflux for 18 h unless otherwise indicated. <sup>†</sup>1.5 equiv. <sup>‡</sup>1.1 equiv. <sup>§</sup>45 h. <sup>||</sup>Method C. <sup>¶</sup>0.05 equiv.

\*Reaction carried out at reflux for 18 h unless otherwise indicated. <sup>†</sup>1.5 equiv. <sup>‡</sup>1.1 equiv. <sup>§</sup>45 h. <sup>||</sup>Method C. <sup>¶</sup>0.05 equiv.

**Table 2: Optimising the rearrangement of **3** to **4****  
 Extended Data Table 2: Optimising the rearrangement of **3** to **4**

entry	Starting material	Base*	T / °C	product	yield	er
1	<i>trans</i> - <b>3-Ala-a</b>	LDA	−78	—	0 (96 <sup>†</sup> )	— <sup>‡</sup>
2	<i>trans</i> - <b>3-Ala-a</b>	LDA	0 - rt	<b>4-Ala-a</b>	95	— <sup>‡</sup>
3	<i>cis</i> - <b>3-Ala-a</b>	LDA	0 - rt	<i>ent</i> - <b>4-Ala-a</b>	92	— <sup>‡</sup>
4 <sup>§</sup>	<i>trans</i> - <b>3-Ala-a</b>	KHMDS	0 - rt	<b>4-Ala-a</b>	95 <sup>  </sup>	>99:1
5 <sup>§</sup>	<i>cis</i> - <b>3-Ala-a</b>	KHMDS	0 - rt	<i>ent</i> - <b>4-Ala-a</b>	99	<1:99

\*1.5 equiv. <sup>†</sup>Yield of *ent*-*cis*-**3-Ala-a** formed by epimerisation. <sup>‡</sup>Not determined. <sup>§</sup>Method A. <sup>||</sup>Reaction on 1.5 g scale.

\*1.5 equiv. <sup>†</sup>Yield of *ent*-*cis*-**3-Ala-a** formed by epimerisation. <sup>‡</sup>Not determined. <sup>§</sup>Method A. <sup>||</sup>Reaction on 1.5 g scale.

**Data availability statement.** Full experimental details and spectroscopic data are provided as supplementary information.

**Supplementary Information** is linked to the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

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### **Author contributions**

DJL, JWW and JC devised the experiments; DJL and JWW carried out the experiments; DJL, JWW and JC analysed the results and wrote the paper.

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