LETTER

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Asymmetric α-arylation of amino acids

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Quaternary amino acids, in which the α-carbon that bears 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[1,2]. In contrast to enantioselective alkylation at this α-carbon, for which there are several methods[3–8], general enantioselective introduction of an aryl substituent at the α-carbon is synthetically challenging[9]. Nonetheless, the resultant α-aryl amino acids and their derivatives are valuable precursors to bioactive molecules[10,11]. Here we describe the synthesis of quaternary α-aryl amino acids from enantiopure amino acid precursors by α-arylation without loss of stereochemical integrity. Our approach relies on the temporary formation of a second stereogenic centre in an *N*′-arylurea adduct[12] of an imidazolidinone derivative[6] 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 valuable transition metals, and enables arylation with electron-rich, electron-poor and heterocyclic substituents. Either enantiomer of the product can be formed from a single amino acid precursor. The method is practical and scalable, and provides the opportunity to produce α-arylated quaternary amino acids in multi-gram quantities.

Among the most practical and widely used methods[13,14] for the synthesis of α-alkylated amino acids are those that use a readily available chiral amino acid both as a starting material and as a source of chirality, using the principle of 'self-regeneration of stereocentres'[6]. This strategy relies on the diastereoselective formation of an imidazolidinone or oxazolidinone, which creates a new stereogenic centre. The configuation of this stereocentre is retained during the formation of a planar amino acid enolate, and it then directs alkylation of the enolate to form a quaternary stereocentre with control over absolute configuration.

The mechanistically unusual[15] N-to-C aryl migration that occurs in anionic derivatives of ureas was first reported in the construction of stereodefined quaternary centres from configurationally stable organolithiums[12], and it has been used to prepare racemic 5,5-disubstituted hydantoins[16]. Stereoselective versions of this hydantoin synthesis using conformational chiral memory[17] or a stoichiometric auxiliary[18] suggested that a practical stereoselective modification of this intramolecular arylation based on imidazolidinone alkylation chemistry might offer a strategy for the synthesis of unavailable enantiopure α-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 Fig. 2a. Treatment of L-AlaNHMe with pivaldehyde and trifluoroacetic acid formed the *trans* diastereoisomer of the imidazolidinone trifluoroacetate salt with good selectivity[19]. In situ chloroformylation with triphosgene in base gave high yields of the *N*-chloroformylimidazolidinones **1-Ala**, as a 4:1 mixture of the *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 (Fig. 2b) and nuclear Overhauser effect experiments (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 (Fig. 2a, Extended Data Table 1, entry 1). The major *trans* diastereoisomer of **1-Ala** (which characteristically and diagnostically exhibited slow N–CO rotation by NMR; Supplementary Information) was much less reactive. The urea *trans*-**3-Ala-a** was formed only when *trans*-**1-Ala** was activated with potassium iodide[20], and a reaction time of 45 h in refluxing CH_2Cl_2 was required for acceptable yields (Fig. 2a, Extended Data Table 1, entries 2–4).

We were now in a position to address the question of the key C–C bond forming step: whether ureas **3-Ala** can undergo the rearrangement we had discovered with other amino acid enolates to provide a means of arylating the amino acid α-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 lithium diisopropylamide (LDA) showed that enolate formation was complete at −78 °C (Extended Data 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 to yield the C-arylated product imidazolidinone **4-Ala-a** from *trans*-**3** and its enantiomer *ent*-**4-Ala-a** from *cis*-**3** (Extended Data Table 2, entries 2, 3). The best yields were obtained on forming the enolate at 0 °C, and even with the milder base potassium bis(trimethylsilyl)amide (KHMDS), **4-Ala-a** was formed in 95% yield from *trans*-**3-Ala** as a single diastereoisomer on a >1-g scale (Extended Data Table 2, entry 4). These conditions (shown as method A in Fig. 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** (Extended Data Table 2, entry 5). In neither case was any trace of the other diastereoisomer of **4-Ala** detectable in the product by ^{1}H NMR, and high-performance liquid chromatography on a chiral stationary phase indicated that the product was essentially enantiomerically pure, with an enantiomeric ratio (e.r.) of >99:1.

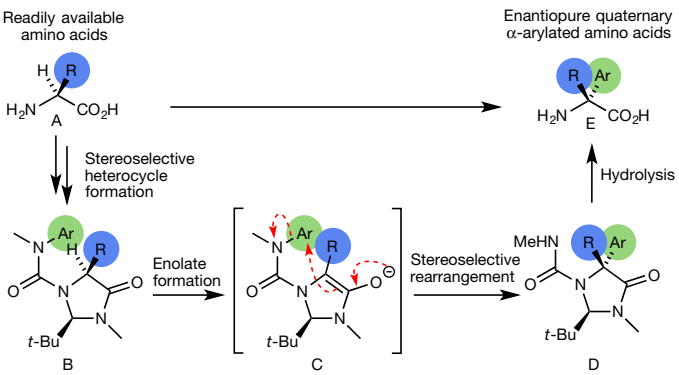

Fig. 1 | Stereoselective arylation of amino acids. Our strategy for stereoselective arylation of amino acids by way of imidazolidinyl ureas is shown. An amino acid (A) is converted diastereoselectively into an imidazolidinone (B) carrying a pendent urea function. Treatment with base forms an enolate (C) in which the aromatic substituent (Ar) of the urea 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) provides the quaternary α-aryl amino acid (E).

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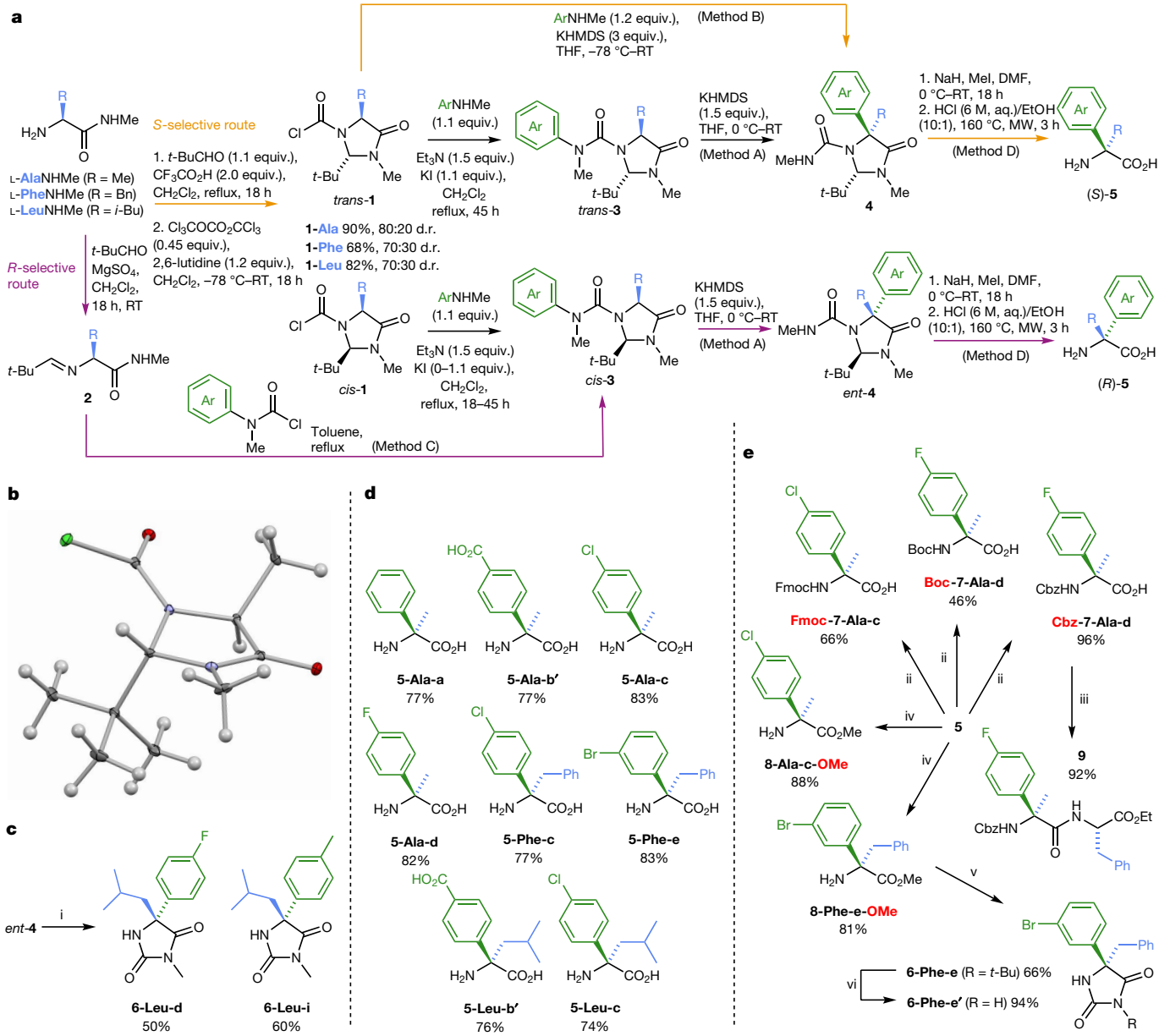

Fig. 2 | Arylation of amino acids by way of imidazolidinone ureas. **a**, Synthetic pathways from L-amino acids to quaternary α-arylated amino acids **5** by way of *N*-chloroformylimidazolidinones **1** or imines **2**, *N*′-aryl imidazolinyl ureas **3**, and C-aryl imidazolidinones **4**. The sequence shown by the orange arrows starting from **1** constitutes an *S*-selective route to **5** from an L-amino acid, whereas the sequence shown by the purple arrows from **2** constitutes an *R*-selective route from an L-amino acid. DMF, dimethylformamide; MW, microwave; RT, room temperature. **b**, The stereochemistry of *trans*-**1**-**Ala** is confirmed by X-ray crystallography. **c**, Representative α-arylated hydantoins formed by hydrolysis of *ent*-**4**. Conditions: i, HCl (6 M, aq.), 130 °C (sealed tube), 18 h. **d**, Yields of representative α-arylated amino acids **5** formed by the methylation and hydrolysis of **4**. **e**, Derivatization of representative quaternary α-arylated amino acids **5** by *N*-protection, peptide coupling, esterification or hydantoin formation. Conditions: ii, 1. *N*-Methyl-*N*-(trimethylsilyl) trifluoroacetamide, CH_2Cl_2, reflux, 4 h; 2. CbzOSu or Boc_2O or FmocOSu (OSu, *N*-hydroxysuccinimide), CH_2Cl_2, RT, 16 h; 3. MeOH, RT, 15 min; iii, 1. K-Oxyma, EDC·HCl (EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide), *i*-Pr_2NEt, DMF, 0 °C–RT, 15 min; 2. L-Phe-OEt·HCl, *N*,*N*-diisopropylethylamine, 72 h; iv, Me_3SiCHN_2, benzene/MeOH (4:1), RT, 18 h; v, 1. *t*-BuNCO, CH_2Cl_2, reflux, 18 h; 2. *t*-BuOK, THF, RT, 18 h; vi, HBr, acetic acid (1:1), 120 °C, 18 h.

Either enantiomer of the product **4**-**Ala** could be formed from the same L-Ala starting material, simply by the choice of route. However, some work on the synthesis of **3** was still needed for this to become a general method for the arylation of amino acids other than alanine. Two problems remained: first, although *cis*-**3**-**Phe** was successfully formed from *cis*-**1** in the presence of KI (Extended Data Table 1, entry 5), *cis*-**1** was generally available only in impractically small quantities as it is formed as the minor diastereoisomer in the preceding chloroformylation step. Second, 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 alanine: attempted acylations using *trans*-**1**-**Phe** were unproductive even when using KI as an activator (Extended Data Table 1, entry 6).

A more robust synthesis of *trans*-**4** was obtained 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** (Extended Data Table 1, entry 6), reaction of *trans*-**1**-**Ala**, *trans*-**1**-**Phe** or *trans*-**1**-**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**. Optimized conditions for this one-pot procedure (labelled method B

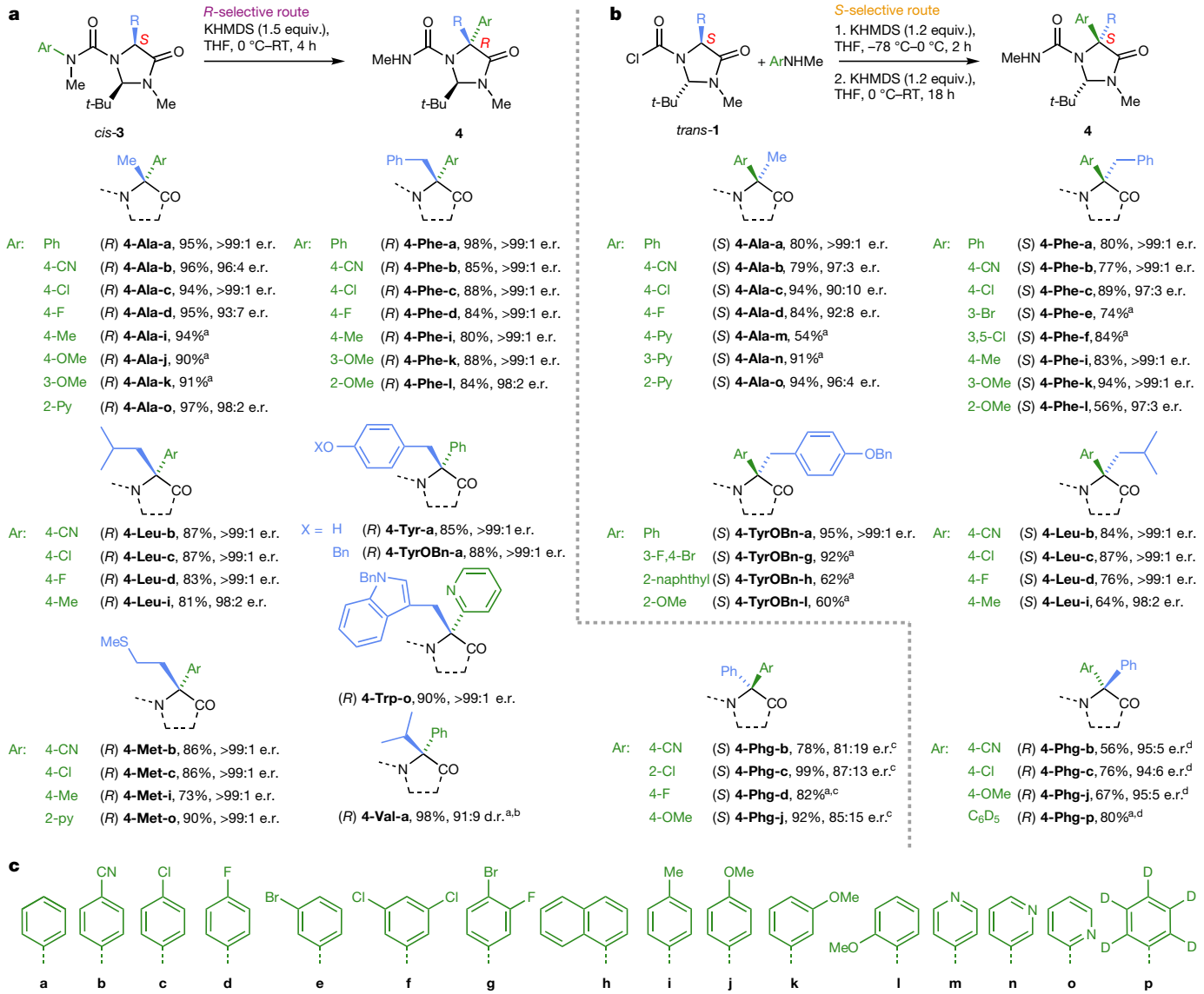

Fig. 3 | Scope of the imidazolidinone arylation: amino acids and migrating groups. a, Product structures, yields and e.r. from use of the optimized *R*-selective route via L-amino-acid-derived imidazolidinones *cis*-**3**. Ar indicates either the aryl substituent itself or the substituent(s) on a phenyl ring. **b**, Product structures, yields and e.r. from use of the optimized *S*-selective route via L-amino-acid-derived imidazolidinones *trans*-**1**. **c**, Structures of the aryl substituents introduced by these methods. [a]e.r. not determined; [b]$LiNEt_2$ 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. [c]D-Phenylglycine was used as starting material, so product has *S* absolute configuration. [d]D-Phenylglycine was used as starting material, so product has *R* absolute configuration.

in Fig. 2a) involved two separate additions of KHMDS. Method B provided an efficient synthesis of an array of products, including **4**-**Ala**, **4**-**Phe** and **4**-**Leu**, which bore a representative selection of substituted aryl rings in high yield and high diastereoselectivity (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. It has been shown that, whereas *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 cyclization of the hindered, planar *N*-acyliminium intermediate[21]. We found that urea *cis*-**3**-**Ala** was indeed formed when the imine **2**-**Ala** was acylated with *N*-methyl-*N*-phenylcarbamoyl chloride (Fig. 2a, Extended Data 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% 4-dimethylaminopyridine (entries 10, 11), but with stoichiometric Et_3N no product was obtained (entry 9). We assume that under these conditions of nucleophilic catalysis, cyclization 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** (Supplementary Information). These imidazolidinone substrates were subjected to the conditions (method A) previously optimized 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 by the orange and purple arrows in Fig. 2a thus provide enantiocomplementary syntheses of 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 α-arylated amino acids **5** by hydrolysis under acidic 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

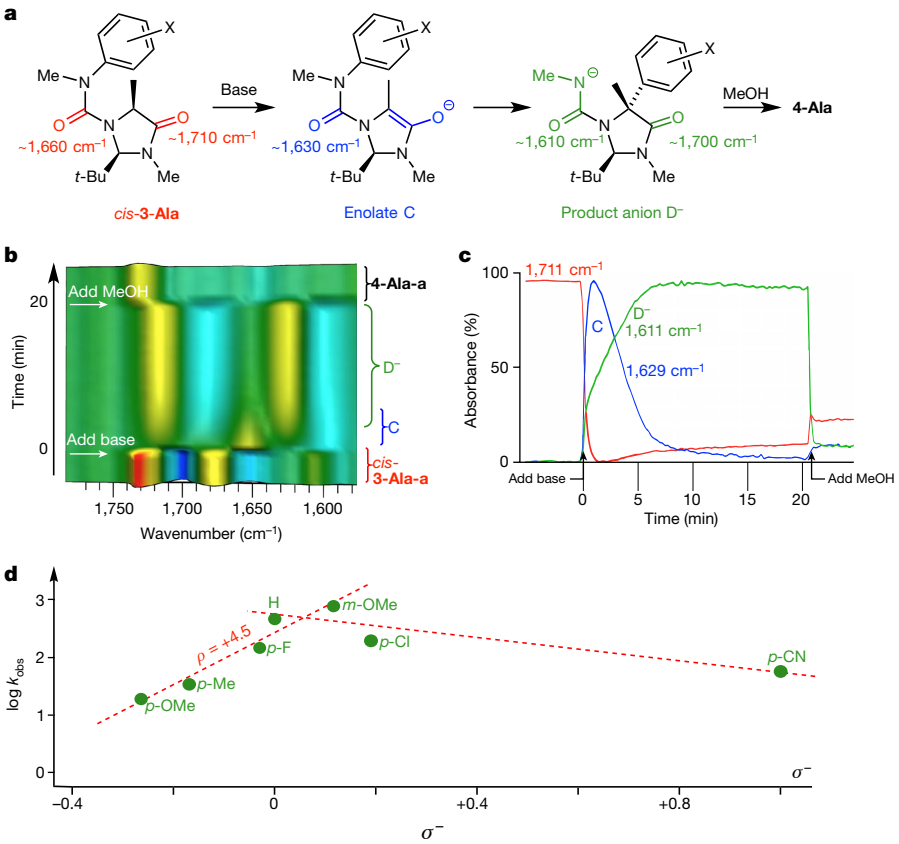

Fig. 4 | Mechanism of the rearrangement. **a**, Proposed reaction pathway, with approximate C=O stretching frequencies. **b**, In situ infrared trace (first-derivative plot) of the reaction of *cis*-**3**-**Ala**-**a**, showing diagnostic changes in carbonyl-stretching frequencies. **c**, Plot of absorbance against time for peaks at 1,711 cm^{-1} (red, starting material), 1,629 cm^{-1} (blue, enolate (C)) and 1,611 cm^{-1} (green, product anion (D^-)). **d**, Hammett plot of logk_{obs} against σ^-, consistent with rate-determining rearrangement for electron-rich rings and rate-determining deprotonation for electron-deficient rings. The gradient of the electron-rich domain on the left of the plot, $\rho = +4.5$, is consistent with substantial charge build-up on the aryl substituent during the rearrangement.

(Fig. 2a, method D, Fig. 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[10].

Hydrolysis without preliminary *N*-methylation led to competitive formation of the corresponding *N*-methylhydantoins **6** in moderate yield (Fig. 2c) owing to cyclization 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[2]. A more versatile synthesis of **6** was obtained 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 acidic conditions (Fig. 2e).

Derivatives of the arylated amino acids that are of value in synthetic procedures such as peptide formation were also formed from **5** (Fig. 2e). Protection of the amino or carboxyl group gave the carboxybenzyl (Cbz)-, *tert*-butyloxycarbonyl (Boc)- or fluorenylmethyloxycarbonyl (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.

After showing 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 the scope to the synthesis of other amino acids, and exploring the scope of migrating aryl groups that can be tolerated by the method. The optimal conditions of the *S*-selective route and the *R*-selective route were applied to a range of starting materials that were derived from amino acids, and the successful outcomes of these reactions are summarized in Fig. 3.

Halogenated (**c**–**g**) rings, even those bearing bromo substituents, rearranged without evidence of dehalogenation or benzyne formation. Sterically hindered *ortho*-substituted (**l**) and 1-naphthyl rings (**h**) also rearranged in good yield. Despite the fact that the rearrangement is formally an intramolecular nucleophilic aromatic substitution (S_NAr) 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 alanine, phenylalanine and leucine, the functionalized side chains of methionine, tyrosine and tryptophan were tolerated, with arylation of tyrosine being successful even without the protection of its hydroxyl group. Phenylglycine (Phg) was also arylated, enabling the enantioselective synthesis of chiral diaryl glycine derivatives **4**-**Phg** (including the enantioselectively deuterated **4**-**Phg**-**p**). With phenylglycine, it was necessary to use method B (starting from *trans*-**1**-**Phg**) to ensure high enantiomeric ratios, as its acidifying side chain evidently leads to some racemization in the synthesis of *cis*-**3**-**Phg** via imine **2**-**Phg**. Arylation of the sterically hindered **3**-**Val** failed with KHMDS, but rearrangement of **3**-**Val**-**a** to **4**-**Val**-**a** proceeded in excellent yield with lithium diethylamide, a more powerful and less bulky base. A slight loss in diastereoselectivity was seen in this reaction, possibly due to the more demanding steric requirements of a transition state in which the *tert*-butyl and isopropyl groups are both on the same side of the imidazolidinone ring.

The mechanism by which the enolate of **3** forms **4** is intriguing. The reaction bears some similarity to the Smiles and Truce–Smiles rearrangements[22,23], 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 ρ, and we explored the kinetics of the reaction by in situ infrared spectroscopy in order to estimate a value of ρ for the rearrangement.

Preliminary studies by infrared spectroscopy using *cis*-**3**-**Ala**-**a** under the optimized conditions for the reaction (1.5 equiv. KHMDS in tetrahydrofuran (THF) at room temperature) revealed no reaction intermediates, which indicates that rearrangement is faster than enolate formation at room temperature. Changing the base to LDA and carrying out the rearrangement at −20 °C decreased the rate of both deprotonation and rearrangement, and revealed an intermediate on the reaction pathway (Fig. 4a, b). This intermediate was identified

as the enolate C (Fig. 4a), on the basis that it has no C=O stretching absorption corresponding to an amide carbonyl group (1,710 cm^{-1} in *cis*-**3**-**Ala**-**a**), but retains the urea (1,630 cm^{-1}) and aromatic (1,500–1,600 cm^{-1}) bands. The rate of decay of this intermediate was identical for both *cis*-**3**-**Ala**-**a** and *trans*-**3**-**Ala**-**a**, which confirms that it is a common intermediate from both diastereoisomers, and treatment of the isolated product with LDA gave an infrared spectrum identical to that of the species present at the end of the reaction, identifying it as the product anion D^- (Fig. 4a). Confirmation that the reaction is intramolecular was provided by a crossover 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** (Supplementary Information).

A Hammett plot was constructed by treating a series of imidazolidinones **3**-**Ala** that bore a selection of aryl substituents with an excess (5 equiv.) of LDA at −20 °C, and the formation of the product anion D^- was monitored using its characteristic infrared bands at around 1,690 and 1,630 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 $\ln([D^-]_\infty - [D^-])$ against time gave a rate constant k_{obs} for each substrate (Fig. 4c). A Hammett plot of $\log k_{obs}$ against the substituent constant σ^- 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 infrared spectroscopy during the rearrangement of **3**-**Ala**-**b** or **3**-**Ala**-**c**). For the electron-rich domain of the plot, the value of ρ is +4.5, consistent with substantial build-up of negative charge on the migrating ring during the reaction. This ρ value is nonetheless smaller in magnitude than those of 'classical' intermolecular S_NAr reactions[24,25], which possibly indicates that the reaction proceeds without the intermediacy of an anionic Meisenheimer complex[26–28]. 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[29] must enforce attack of the enolate on the ring, irrespective of the inability of the ring to stabilize a negative charge[30]. As a consequence, the aryl ring behaves as an electrophile, much as alkylating agents do in 'classical' reactions of enolates. This use of conformational restriction to induce electrophilic reactivity in electron-rich substituents not only makes generally available this otherwise elusive class of modified amino acids, but also has the potential for wider application in synthesis.

Data availability

Full experimental details and spectroscopic data are provided as Supplementary Information.

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Additional information
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Extended Data Table 1 | Optimizing the synthesis of 3

entry	starting materials	solvent[a]	base[b]	additive	product	yield
1	*cis*-**1-Ala** + PhNHMe	CH_2Cl_2	Et_3N	–	*cis*-**3-Ala-a**	95
2	*trans*-**1-Ala** + PhNHMe	CH_2Cl_2	Et_3N	–	–	0
3	*trans*-**1-Ala** + PhNHMe	CH_2Cl_2	Et_3N	KI[c]	*trans*-**3-Ala-a**	40
4	*trans*-**1-Ala** + PhNHMe	CH_2Cl_2[d]	Et_3N	KI[c]	*trans*-**3-Ala-a**	86
5	*cis*-**1-Phe** + PhNHMe	CH_2Cl_2	Et_3N	KI[c]	*cis*-**3-Phe-a**	90
6	*trans*-**1-Phe** + PhNHMe	CH_2Cl_2	Et_3N	KI[c]	*trans*-**3-Phe-a**	20
7	**2-Ala** + PhMeNCOCl	MeCN	–	–	*cis*-**3-Ala-a**	50
8	**2-Ala** + PhMeNCOCl	PhMe	–	–	*cis*-**3-Ala-a**	65
9	**2-Ala** + PhMeNCOCl	PhMe	Et_3N	–	*cis*-**3-Ala-a**	<5
10[e]	**2-Ala** + PhMeNCOCl	PhMe	–	DMAP[f]	*cis*-**3-Ala-a**	88
11	**2-Ala** + PhMeNCOCl	$(CH_2Cl_2)_2$	–	DMAP[f]	*cis*-**3-Ala-a**	85

[a]Reaction carried out at reflux for 18 h unless otherwise indicated.
[b]1.5 equiv.
[c]1.1 equiv.
[d]45 h.
[e]Method C.
[f]0.05 equiv.

Extended Data Table 2 | Optimizing the rearrangement of 3 to 4

entry	Starting material	Base[a]	*T* / °C	product	yield	*er*
1	*trans*-**3-Ala-a**	LDA	–78	–	0 (96[b])	–[c]
2	*trans*-**3-Ala-a**	LDA	0 - rt	**4-Ala-a**	95	–[c]
3	*cis*-**3-Ala-a**	LDA	0 - rt	*ent*-**4-Ala-a**	92	–[c]
4[d]	*trans*-**3-Ala-a**	KHMDS	0 - rt	**4-Ala-a**	95[e]	>99:1
5[d]	*cis*-**3-Ala-a**	KHMDS	0 - rt	*ent*-**4-Ala-a**	99	<1:99

[a]1.5 equiv.
[b]Yield of *ent-cis*-**3-Ala-a** formed by epimerization.
[c]Not determined.
[d]Method A.
[e]Reaction on 1.5-g scale.