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# Enantioselective synthesis of non-proteinogenic 2-arylallyl-α-amino acids via Pd/In catalytic cascades

Ronald Grigg,[a,*] Shaun McCaffrey,[a] Visuvanathar Sridharan,[a] Colin W. G. Fishwick,[a] Colin Kilner,[a] Stewart Korn,[b] Kevin Bailey[b] and John Blacker[b]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, University of Leeds, Leeds LS2 9JT, UK*
[b]*Avecia Ltd, Leeds Road, Huddersfield, West Yorkshire HD2 1GA, UK*

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**Abstract**—An efficient synthesis of both *R*- and *S*-enantiomers of 2-arylallyl-α-amino acids via a diastereoselective Pd/In mediated catalytic allylation of chiral *N*-sulfinyl-α-imino esters is described. The potential for further enhancement of molecular complexity and creating contiguous chiral centres by interfacing these processes with catalytic cyclisation–anion capture methodology is demonstrated.


## 1. Introduction

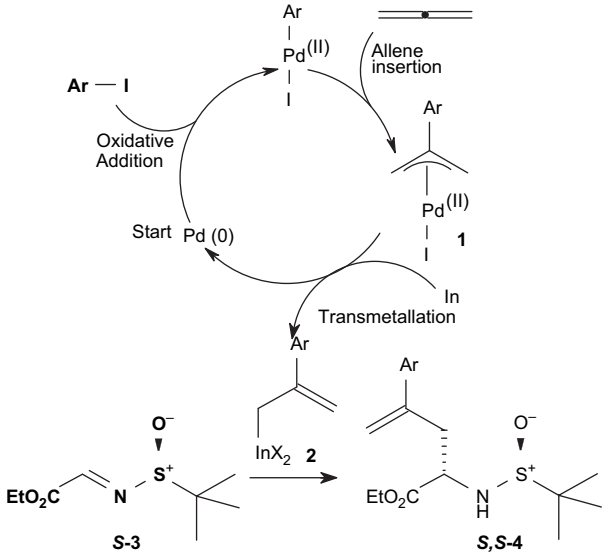
The synthesis of peptides and proteins containing non-natural α-amino acids vastly increases the structural and chemical diversity of polypeptides.

Novel α-amino acid side-chains and the availability of both *R*- and *S*-stereoisomers enable tuning of pharmacokinetics, formation of β-sheets and other peptide structural motifs that effect biological activity and structural properties.

The synthesis of 'designer' peptidomimetics, incorporating and/or modifying the beneficial aspects of the parent polypeptides whilst also possessing enhanced metabolic stability and/or improved pharmacokinetics, is an area of burgeoning interest.[1–3]

The asymmetric alkylation of glycine cation equivalents is a general, efficient route to non-proteinogenic α-amino acid derivatives. Previously, our group reported highly regio- and diastereoselective Pd/In mediated cascade allylations of carbonyl compounds including a highly stereoselective allylation of chiral *N*-sulfinyl aldimines.[4–10] We now report further applications of the *tert*-butyl sulfinyl chiral auxilliary, which has been widely used in the synthesis of chiral amines including 1,2-amino alcohols and α- and β-amino acids,[11–13] to a new approach to unusual α-amino acids.

The Pd/In bimetallic cascade process involves generation of an electrophilic π-allyl palladium species **1** that undergoes transmetallation in the presence of indium, furnishing nucleophilic $\eta^1$-allyl indium species **2**. Allylation of the enantiopure *N*-sulfinyl-α-imino ester **3**, affords *N*-sulfinyl-α-alkyl-α-amino esters **4** as single diastereoisomer (Scheme 1). Initial experiments employing iodobenzene and a catalyst system comprising of 10 mol % $Pd(OAc)_2$, 20 mol % tris-2-furyl phosphine and 20 mol % CuI in DMF at 40 °C confirmed these expectations (Table 1, entry 1).




**Scheme 1**. Reaction mechanism. Reagents and conditions: (i) ArI (0.75 mmol), allene (1 atm), In (0.75 mmol), $Pd(OAc)_2$ (10 mol %), tri-2-furyl phosphine (20 mol %), CuI (20 mol %), piperidine (0.5 mmol), DMF (20 ml/mmol), 40 °C, 24 h; (ii) 4 M HCl/dioxane (5 mol equiv), EtOH (10 ml/mmol), 30 min, rt, NaOH (2 mol equiv), 1:1 v/v EtOH/$H_2O$ (10 ml/mmol) reflux, 2 h.

* Corresponding author. Tel.: +44 113 3436501; fax: +44 113 3436530; e-mail: r.grigg@leeds.ac.uk

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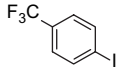
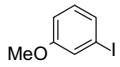
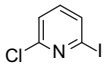
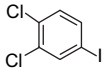
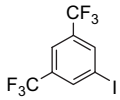
**Table 1**. Bimetallic cascade synthesis of chiral **4a–h** and **5a–h**[a]

| Entry | ArI | Cascade product | | Amino acid | |
|---|---|---|---|---|---|
| | | Configuration | Yield (%)[b] | Configuration | Yield (%)[c] |
| 1 |  | *S,S*-**4a** | 92 | *S*-**5a** | 100 |
| | | *R,R*-**4a** | 80 | *R*-**5a** | 100 |
| 2 |  | *S,S*-**4b** | 69 | *S*-**5b** | — |
| | | *R,R*-**4b** | 55 | *R*-**5b** | 100 |
| 3 |  | *S,S*-**4c** | 68 | *S*-**5c** | 50 |
| | | *R,R*-**4c** | 68 | *R*-**5c** | 54 |
| 4 |  | *S,S*-**4d** | 54 | *S*-**5d** | 99 |
| | | *R,R*-**4d** | 49 | *R*-**5d** | 99 |
| 5 |  | *S,S*-**4e** | 72 | *S*-**5e** | 97 |
| | | *R,R*-**4e** | 67 | *R*-**5e** | 80 |
| 6 |  | *S,S*-**4f** | 52 | *S*-**5f** | 85 |
| | | *R,R*-**4f** | 69 | *R*-**5f** | 79 |
| 7 |  | *S,S*-**4g** | 73 | *S*-**5g** | 73 |
| | | *R,R*-**4g** | 74 | *R*-**5g** | 82 |
| 8 |  | *S,S*-**4h** | 69 | *S*-**5h** | 89 |
| | | *R,R*-**4h** | 76 | *R*-**5h** | 68 |

[a] Conditions as for Scheme 1.
[b] Isolated yield.
[c] Isolated overall yield for the two-step deprotection.

The scope of the reaction was explored through a series of aryl iodides (Table 1). X-ray crystal structures of one such pair *S,S*-**6** and *R,R*-**6** (Fig. 1), derived by partial deprotection of *S,S*-**4g** and *R,R*-**4g**, established that the *S*-sulfinimine engenders *S* stereochemistry at the new chiral centre and the *R*-sulfinimine provides *R* stereochemistry at the new chiral centre.[14] Non-proteinogenic α-amino acids **5** are obtained in good to excellent yield (Table 1) from **4** via a two-step deprotection process (Scheme 2).

A rationale for the stereochemical outcome of the cascade **3**→**4** is summarised in Figure 2. The four possible Zimmerman–Traxler, chair-like transition states **7–10** have been modelled using semi-empirical calculations.[15] These correspond to additions of the allyl indium intermediate to either the *re* or *si* face of the *S*-sulfoximine, each of which can

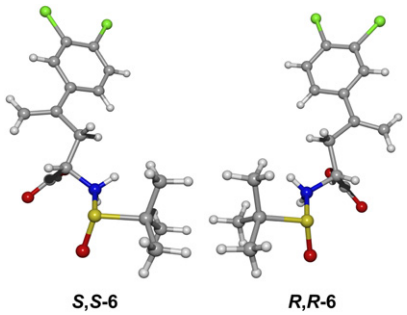
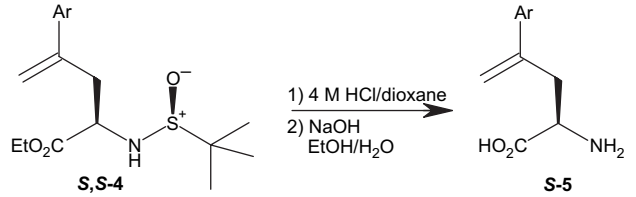


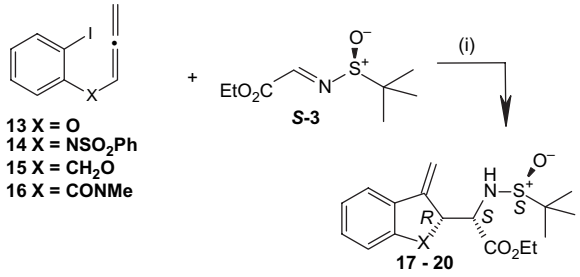

**Figure 1**. X-ray crystal structures of a matched pair of enantiomers.




**Scheme 2**. Deprotection of *N*-sulfinyl esters. Cleavage of the chiral sulfinyl auxilliary is carried out first by treatment with 4 M HCl in dioxane (5 mol equiv) for 30 min. Following the removal of the solvent the crude material is treated with 1 M aqueous NaOH solution (2 mol equiv) in a 1:1 v/v EtOH/$H_2O$ under reflux for 2 h. The amino acids **5a–h** are isolated using an Amberlyst $H^+$ ion exchange resin (Table 1).

involve two possible chair-like arrangements. The heat of formation ($\Delta H_f$) and imaginary vibrational frequencies ($\nu_i$) for transition states corresponding to additions to the *S*-sulfoximine indicate a marked preference for transition state **10**, which locates the ester moiety axially. Closer inspection of this transition state reveals that the ester carbonyl oxygen is located near to the indium atom (O–In distance of 2.80 Å) indicating coordination to the indium atom. This transition state leads to the product possessing *S* stereochemistry at the newly created chiral centre. Interestingly, transition state **10** also locates the sulfoxide oxygen near to the metal centre (at a distance of 2.75 Å) and this, although now involves a four-membered ring, may also further stabilise the transition state. This type of chelation appears to be energetically important as the next most favourable transition state **8** locates the sulfoxide oxygen close to the metal centre at a distance of 2.75 Å. (Note: the calculations employed parameters for In(III) although the valence state of the In in this chemistry is not yet established.)

To further extend the scope of our chemistry, we have utilised bifunctional aryl iodide/allenes **13–16** (Scheme 3) allowing access to our catalytic cyclisation-anion capture methodology.[16] The cyclisation–allylation reaction is entirely regio- and diastereoselective generating two contiguous chiral centres with complete stereocontrol, affording **17–20** in moderate to good yield (Table 2).




**Scheme 3**. Tandem cyclisation–imine capture cascade. Reagents and conditions: (i) ArI (0.75 mmol), In (0.75 mmol), $Pd(OAc)_2$ (10 mol %), tri-2-furyl phosphine (20 mol %), CuI (20 mol %), piperidine (0.5 mmol), DMF (20 ml/mmol), 80 °C, 24 h.

A matched pair of X-ray crystal structures *S,S,R*-**18** and *R,R,S*-**18**[14] established that the *R*-sulfinimine engenders *R* stereochemistry at the 5-position and *S* stereochemistry at the 6-position (Table 2, entries 3 and 4, Fig. 3). Semi-empirical calculations reveal a similar trend to those described above. In this case, four chair-like transition states