Chiral Auxiliaries

Pseudoephedrine-Directed Asymmetric α-Arylation of α-Amino Acid Derivatives**

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Abstract: Available α -amino acids undergo arylation at their α position in an enantioselective manner on treatment with base of N'-aryl urea derivatives ligated to pseudoephedrine as a chiral auxiliary. In situ silylation and enolization induces diastereoselective migration of the N'-aryl group to the α position of the amino acid, followed by ring closure to a hydantoin with concomitant explusion of the recyclable auxiliary. The hydrolysis of the hydantoin products provides derivatives of quaternary amino acids. The arylation avoids the use of heavy-metal additives, and is successful with a range of amino acids and with aryl rings of varying electronic character.

he central role of amino acids in nature makes them one of the most important targets for modification in medicinal chemistry and chemical biology.^[1] One modification in particular, the stereoselective functionalization of the α carbon atom to prepare quaternary α -amino acids and their derivatives, has led to compounds of major structural and medicinal significance.^[2]

A range of methods for the asymmetric α -alkylation of readily available amino acids makes simple quaternary amino acids bearing α -alkyl groups readily accessible.^[3–9] There are far fewer options for the asymmetric introduction of aryl rings^[10,11] to the α -carbon atom of α -amino acids to make quaternary α -arylated amino acids, and those that exist suffer from severe limitations in scope. Racemic α -arylations have been achieved through Pd^[12–14] or Fe^[15] catalyzed reactions of enolates to form heterocyclic amino acid derivatives, with an asymmetric version requiring a complex multi-step sequence.^[16] Electron-deficient rings may be introduced intra-^[17–20] or intermolecularly^[21–23] by stereoselective aryne or S_NAr chemistry. Maruoka et al.^[24] achieved an asymmetric phase-transfer arylation with Cr complexes of electron-rich arenes.

We previously reported^[25] a racemic approach to the synthesis of α -aryl amino acids that makes use of the rearrangement of N-aryl urea derivatives^[26–30] of amino acid

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enolates with migration of an aromatic ring from N to C. The reaction formally involves an intramolecular nucleophilic aromatic substitution reaction,^[31,32] but is much more general with regard to ring electronics than a typical S_NAr reaction.^[33] Kawabata et al.^[34] simultaneously reported a chiral memory effect in a related reaction that allowed certain members of the class of α -aryl α -amino acid derivatives to be prepared with good enantioselectivity.

Aiming to solve the problem of asymmetric arylation of amino acids, particularly with electron-rich rings, we decided to start from Myers' very general methods for asymmetric alkylation,^[8,9,35,36] with the goal of developing an intramolecular asymmetric α -arylation of amino acids employing (*S*,*S*)-pseudoephedrine (**2**) as an auxiliary (Scheme 1). Coupling **2** to the urea derivative **1** of *N*-methyl-L-Ala yielded the alanine amide **3**, typically as a 4:1–5:1 mixture of diastereoisomers.



Scheme 1. Enantioselective arylation of an amino acid derivative.

The results of forming the enolate 4 by treatment of 3 with an excess (>2 equiv) of base are shown in Table 1. A change in the ratio of diastereoisomers of the starting material provided evidence that deprotonation by alkyllithium reagents gave an enolate at temperatures above -78°C (Table 1, entry 1), and fast warming of the enolate to room temperature gave the hydantoin 6 as its S enantiomer with moderate enantiomeric enrichment (Table 1, entries 1 and 2; see below for stereochemical determination). Presumably, the enolate 4 rearranges to 5 with migration of the phenyl ring to the α -carbon atom of the alanine residue, and the hydantoin ${\bf 6}$ is formed by ring closure with expulsion of the auxiliary 2. HMDS bases gave poorer yields and selectivity (Table 1, entries 4-6), but selectivity was markedly improved in the presence of LiCl (entries 7-9), a result consistent with the work of Myers et al.^[35] Yields were highest when lithium amide bases (LDA or LiTMP) were used. Under optimum

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Table 1: Rearrangement of alanine derivative 3 to hydantoin (S)-6.

Entry	Base (equiv)	Additive (equiv)	Yield of 6 [%]	e.r. of 6 (<i>R:S</i>)
1	sBuLi (3)	DMPU (20)	0, ^[a]	_, ^[a,c]
			47 ^[b]	22:78 ^[b]
2	<i>n</i> BuLi (3)	-	68	22:78
3	LDA (3)	-	56	23:77
4	KHMDS (3)	-	41	60:40
5	NaHMDS (3)	-	50	39:61
6	LiHMDS (3)	-	44	32:68
7	<i>n</i> BuLi (4.5)	LiCl (12)	49	8:92
8	LDA (3)	LiCl (12)	66, ^[d]	10:90, ^[d]
			72 ^[e]	12:88 ^[e]
9	LiTMP (3)	LiCl (12)	64	8:92

General conditions: $-78 \rightarrow +20$ °C in THF (0.1 M). [a] -78 °C for 7 h, slow warming to +20 °C. [b] -78 °C for 0.5 h, rapid warming to +20 °C. [c] Recovered 3 had d.r. of 85:15 at -78 °C and of 70:30 at RT. [d] 0.1 mmol. [e] 0.32 mmol.

conditions, the hydantoin 6 was obtained in about 70% yield and 90:10 e.r.

The doubly N-methylated hydantoin product 6 proved extremely resistant to hydrolysis^[25] to the corresponding quaternary N-methylated amino acid, so we modified the substrates 3 with the aim of rearranging their N-unsubstituted analogues 7 (Scheme 2). These were conveniently obtained as single diastereoisomers by acylating L-AlaOEt or L-MetOMe with N-phenyl-N-methyl carbamoyl chloride, ester hydrolysis, and coupling the resulting urea with (S,S)-pseudoephedrine **(2)**.

Treatment of 7a with four equivalents of LDA or LiTMP in the presence of LiCl gave the corresponding hydantoin 9a in moderate yield, but as a racemic mixture (Table 2, entries 1 and 2). Reasoning that N substitution may be essential for stereoselective rearrangements, we added trimethylsilyl chlo-



Scheme 2. Optimization of the enantioselective rearrangement.

Table 2: Rearrangement of unsubstituted amino acid derivatives 7 a,b to hydantoins 9a,b.

Entry	SM	Base (equiv)	equiv of LiCl	equiv of Me₃SiCl	(R)- 9 , Yield ^[a] [%]	e.r. of 9 (R:S)
1	7 a	LDA (4)	7	0	9a , 54	50:50
2	7 a	LiTMP (4)	7	0	9 a, 43	55:45
3	7 a	LDA (4)	7	1	9 a, 60	75:25
4	7 a	LDA (4)	7	2 ^[b]	9 a, 65 ^[b]	92:8
5	7 a	LDA (4)	7	3 or 4	0	_[c]
6	7 a	KHMDS (4)	-	2	0	_
7	10 a	LDA (3)	7	1	9 a, 50 ^[d]	86:14
8	10 a	LDA (3)	7	2	0	_
9	10b	LDA (4)	7	2	9a , 68	10:90
10	10 c	LDA (4)	0	2	9 a, 82 ^[e]	79:21
11	10 d	LDA (4)	7	2	9 a, 32	91:9
12	10e	LDA (4)	0	1	0	_
13	7 b	LDA (4)	7	2	9b , 24	92:8
14	7 b	LDA (2+2) ^[f]	_	2.1	9b , 70 ^[g]	93:7

[a] After quenching with HCl, except entry 14. [b] Slightly lower yield and e.r. obtained with Me₃SiOTf; with TBDMSOTf or TBDMSCI the reaction failed to reach completion and gave lower e.r. [c] Starting material (SM) recovered (accompanied by an epimer when 4 equiv Me_3SiCl were used). [d] Yield determined by NMR spectroscopy. [e] Yield of crude product. [f] LDA (2 equiv) was added to the substrate, followed by Me₃SiCl (2.1 equiv). After 30 min, a further 2 equiv of LDA were added, and after 15 min, the mixture was warmed to room temperature. [g] After quenching with K₂CO₃ in MeOH.

ride to the reaction mixture with the aim of trapping the anionic urea in situ, yet still allowing enolate 8C to form and the rearrangement to take place. With one equivalent of Me₃SiCl, some enantiomeric enrichment was observed (Table 2, entry 3), but with two equivalents of Me₃SiCl, the e.r. of product 9a rose to 92:8 in favor of the R enantiomer (entry 4). The yield of 65% represents the outcome of a multi-step sequence of deprotonation, silvlation, rearrangement, cyclization, and desilylation. Three equivalents or more of Me₃SiCl lowered the yield and led to the recovered starting material as a mixture of epimers (Table 2, entry 5). A screen of other silvlating agents resulted in none that performed better than Me₃SiCl (Table 2, entry 4), and the use of KHMDS gave no product (entry 6).

This dependence of the reaction on the number of equivalents of silylating agent is very informative. As maximal yields and enantiomeric ratios were obtained with two equivalents of Me₃SiCl, we propose that this stoichiometry allows silvlation firstly of the pseudoephedrine hydroxy group and secondly of the urea anion (probably^[37] on the oxygen atom), giving a doubly silvlated intermediate whose deprotonation results in an enolate 8C capable of selective rearrangement. Less than two equivalents of silvlating agent gave lower enantioselectivity, possibly because the corresponding unsilvlated species 8A and/or monosilvlated species 8B may still lead to competing rearrangement, but without selectivity.^[38] We assume that more than two equivalents of Me₃SiCl leads to an unreactive silyl enol ether 8D, whose hydrolysis at work up can therefore return partly epimerized starting material (Table 2, entry 5). Support for this explanation of the need for two equivalents of Me₃SiCl was provided by rearrangement of the alternative starting material 10a, in



which preliminary silulation of the pseudoephedrine auxiliary gave a good e.r. even with one equivalent of Me_3SiCl (Table 2, entry 7), but returned starting material with two equivalents of Me_3SiCl (entry 8).

The other enantiomer of the pseudoephedrine auxiliary gave the epimeric starting material **10b**, which rearranged to (*S*)-**9a** with no evident match/mismatch effects (Table 2, entry 9).^[9,36] Alternative auxiliaries performed less well: ephedrine (**10c**) gave poorer selectivity (Table 2, entry 10); pseudephenamine^[39,40] (**10d**) gave lower yields (entry 11) possibly because of competing benzylic deprotonation^[27] α to the N atom, and Evans' oxazolidinone derivative **10e** was unstable to the reaction conditions (entry 12).

Extension of the optimal conditions summarized in entry 4 of Table 2 for the arylation of alanine to the methionine-derived substrate **7b** gave hydantoin products in equally good enantiomeric ratios, but significantly lower yield (entry 13). The reaction protocol was therefore modified (Table 2, entry 14) to ensure that both the hydroxy group of pseudoephedrine and the N atom of urea were fully silylated before formation of the enolate **8C**. As this reaction no longer takes place through an alkoxide intermediate, we also omitted $\text{LiCl}^{[35]}$ from the reaction mixture. As a consequence, the yield of the hydantoin (*R*)-**9b** increased to 70% and the stereose-lectivity to 93:7 e.r.

These optimized conditions were applied to a range of substrates (**7a–v**, Scheme 3). Each starting material was prepared in three steps from the methyl or ethyl ester of the corresponding amino acid. Acylation with the appropriate carbamoyl chloride^[41] was followed by ester hydrolysis and coupling with pseudoephedrine to give the ureas **7**, which were treated with LDA and Me₃SiCl.

The domino process of silylation, enolization, arylation, and cyclization to give hydantoin derivatives of alanine, methionine, butyrine, n-propylglycine, leucine, lysine, and proline with a phenyl ring (9a-g) or other electron-rich (9i-l) rings proceeded with moderate to good yields, and with high levels of stereoselectivity. Crystallization from chloroform returned (\pm) -9a as a racemate^[42] and evaporation of the mother liquor gave (R)-9a with the enantiomeric ratio enhanced to 99:1. Rearrangement of the more hindered leucine was less clean (and all attempted rearrangements of valine- or phenylglycine-derived ureas failed), suggesting that leucine lies at the limit of the method's tolerance to steric hindrance. Arylation with more electron-deficient rings (9ms), and arylation of pipecolic acid (9h), gave slightly to substantially lower enantioselectivities, and in some cases low yields, even when the non-stereoselective arylations from 11 or 12 were clean reactions. Some substrates (generally those with acidic protons in the β position, **7t**-v) failed to rearrange cleanly,^[43] although the racemic products 9t-v were formed in good yield from 11 or 12.

The superior performance of the pseudoephedrinedirected rearrangement in arylations with electron-rich rings renders this method usefully complementary to other methods for the arylation of amino acid enolates, which perform well only with electron-deficient rings.^[17–22,34] The only method currently available for the asymmetric arylation of amino acids with electron-rich rings requires stoichiometric



Scheme 3. Asymmetric arylation of a range of amino acids. Yields and enantiomeric ratios quoted for hydantoin products **9**. [a] (\pm)-Amino ester used for **7 c**,**d**,**h**,**j**,**t** (which are therefore a diastereoisomeric mixture). [b] LDA used for the racemic rearrangement of **12** to **9 a**–**c**,**e**,**k**,**u**. [c] Representative recovery of pure (*S*,*S*)-pseudoephedrine from the rearrangement of **9 a**. [d] Racemic product obtained from the rearrangement of **7**. [e] **7 n**,**o** synthesized by DSC activation of aminopyridine (see the Supporting Information). [f] Reaction performed with 3.1 equiv Me₃SiCl. [g] Attempted rearrangement of **7** returned a complex mixture of products.^[43]



Cr and a large excess of nucleophile.^[24] Even related auxiliary-directed alkylations of amino acids work only with alanine.^[9]

The rearrangement returns the pseudoephedrine auxiliary without the need for a separate hydrolysis step. Recovery of pseudoephedrine from the product mixture is straightforward: washing the crude organic fractions from the rearrangement of **9a** with 1M HCl takes the pseudoephedrine into the aqueous layer, from which it can be recovered in 81% yield (pure by m.p. and $[\alpha]_D$) by basification and extraction.

N-Methylated hydantoins show a range of biological activities.^[44-47] Specifically, hydantoin (R)-9c is the R enantiomer of the anticonvulsant mephenytoin. Our method provides the first asymmetric synthesis of this compound: previous approaches used resolution of chiral precursors.^[48-50] Nonetheless, the hydantoins could be straightforwardly and nearly quantitatively converted to their parent quaternary amino acids by basic hydrolysis (Scheme 3 shows three representative examples). The amino acids **13** were conveniently isolated as their methyl esters **14** in excellent yield.

The absolute configuration of the products 9 of the rearrangement was confirmed by comparison with reported data. Optical rotation confirmed the configuration of (R)-14a $([\alpha]_{D}^{21} = -46.4 (c = 0.5, MeOH, 92:8 e.r.); lit.^{[51]} - 51.8, (c = 0$ MeOH)), and (R)-9c was identical to (R)-mephenytoin $([\alpha]_{D}^{21} = -71.4 \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ EtOH}; 91:9 \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ e.r.}); \text{ e.r.}); \text{ lit.}^{[49]} -101.6, \ (c = 0.14, \text{ e.r.}); \text{ e.r.}$ 0.13, EtOH)). We assume therefore that hydantoins 9 are formed likewise with R configuration using (S,S)-pseudoephedrine, and with S selectivity using (R,R)-pseudoephedrine. The fact that the rearrangements of 3 (Scheme 1) and 7 (Schemes 2 and 3) proceed with opposite stereoselectivity was confirmed by N methylation of (R)-9a (NaH, MeI, 98% yield), which gave a sample of 6, whose optical rotation $\{[\alpha]_{D}^{21} = -88.0 \ (c = 1.0, CHCl_3, 88:12 \text{ e.r.})\}$ was opposite to that $\{[\alpha]_{D}^{21} = +87.6 \ (c = 1.1, \text{ CHCl}_{3}, 12:88 \text{ e.r.})\}$ of the compound produced by the reaction shown in Table 1, entry 8.

Given the sense of stereoselectivity of the arylation of **7**, we propose a transition state for rearrangement of **8**C related to those suggested by Myers for alkylations of amino acids.^[9] Typically, tetrasubstituted enolates of related pseudoephedrine derivatives form with *E* geometry. However, to explain the *R* selectivity of the rearrangement, we propose the reaction pathway shown in Scheme 4, in which chelation of lithium by the electron-rich isourea nitrogen atom during enolate formation generates the *Z* enolate **8**C. Rotation of the urea into a reactive conformation then leads to a lowerface attack on the enolate, providing *R*-configured products.^[52]



Scheme 4. Stereoselective enolate arylation directed by (S,S)-pseudo-ephedrine.

To conclude, the rearrangement of pseudoephedrinecontaining ureas provides a practical method for the asymmetric arylation of readily available amino acids. The method uses no heavy-metal catalysts or additives, and is most successful with electron-rich rings and with amino acids containing saturated side chains. It proceeds through a tandem reaction sequence entailing silyl protection, deprotonation, rearrangement, auxiliary release, and deprotection, all taking place in a single operation. The immediate products are enantioenriched hydantoins that may be converted in high yield to valuable enantioenriched α -arylated quaternary amino esters.

Keywords: amino acids \cdot arylation \cdot chiral auxiliaries \cdot enolates \cdot pseudoephedrine

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