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Geometry-retentive *C*-alkenylation of lithiated α-aminonitriles: quaternary α-alkenyl amino acids and hydantoins

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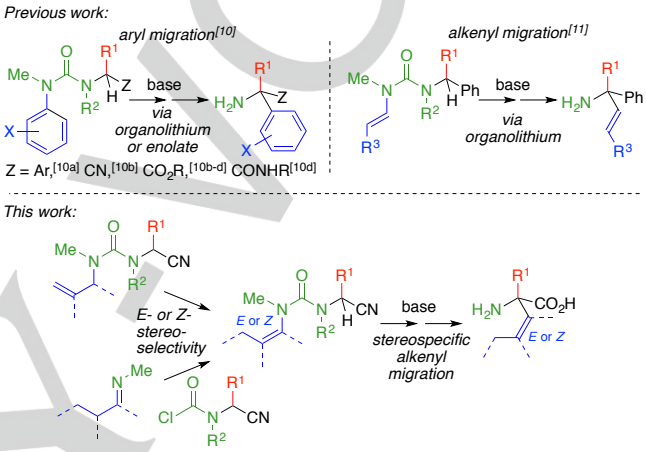
Abstract: *α-Amino nitriles tethered to alkenes through a urea linkage undergo intramolecular C-alkenylation on treatment with base by attack of the lithionitrile derivatives on the N'-alkenyl group. The geometry-retentive alkene shift affords stereospecifically the E or Z isomer of the 5-alkenyl-4-iminohydantoin products from the corresponding starting E- or Z-N'-alkenyl urea, each of which may be formed from the same N-allyl precursor by stereodivergent alkene isomerisation. The reaction, formally a nucleophilic substitution at an sp^2 carbon atom, allows the direct regioselective incorporation of mono-, di-, tri- and tetrasubstituted olefins at the α-carbon of amino acid derivatives. The initially formed 5-alkenyl iminohydantoins may be hydrolysed and oxidatively deprotected to yield hydantoins and unsaturated α-quaternary amino acids.*

Amino acids bearing alkenyl α-substituents are inhibitors of amino acid decarboxylase and transaminase enzymes, being used as antibiotics, anticarcinogens and herbicides.[1] They are also important structurally, allowing *in situ* peptide modification by olefin metathesis.[2] Sterically constrained α,α-disubstituted-α-amino acids (α-quaternary amino acids) are likewise important components of bioactive compounds, and their incorporation into peptides favours helical secondary structures[3] and offers increased resistance to chemical and enzymatic degradation.[4]

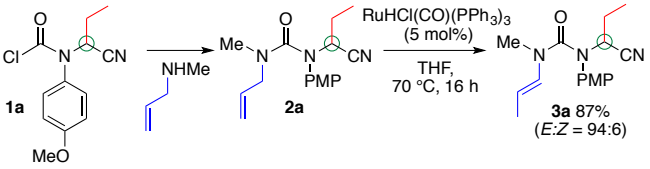
In general, α-quaternary amino acids and their derivatives, such as biologically important 5,5-disubstituted hydantoins,[5] may be made from their tertiary counterparts by alkylation or rearrangement.[6] In addition, a small number of transition-metal-catalyzed methods for the arylation of amino acid derived enolates have recently been developed.[7] However, a general method for the direct α-*C*-alkenylation of amino acids or their derivatives, even in a racemic fashion, is lacking. Existing approaches to α-alkenylated amino acids require activated acetylenes as precursors,[8] or install the alkene by a multi-step procedure.[9]

In this paper we present a method for introducing a *C*-alkenyl substituent into an α-amino acid derivative by using a urea tether to link an α-amino nitrile with an *N'*-alkenyl substituent. Treatment of this ureidonitrile with base promotes migration of the *N'*-alkenyl substituent from nitrogen to carbon, in a reaction that bears comparison with other reported migrations of unsaturated substituents across the urea function (Scheme 1).[10,11] Four alternative methods were used to make the starting N'-alkenylureas, each having characteristic *E* or *Z* stereoselectivity. The migration step was not only highly tolerant of steric hindrance, but also proceeds with retention of double bond geometry, allowing the synthesis of both *E* and *Z*-alkenyl amino acids.



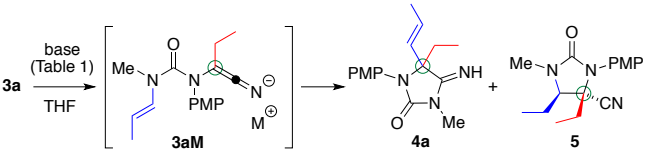
Scheme 1. Alkenylation of an aminonitrile by N to C migration in a urea derivative

The study began with *N'*-alkenyl urea *E*-**3a**, made by *E*-selective Ru-catalysed rearrangement of *N*-allyl urea **2a**,[12,13] formed from Strecker-derived carbamoyl chloride **1a** (Scheme 2). Table 1 shows the results of treating *E*-**3a** with base, with the aim of migrating the alkenyl group to the position α to the nitrile.



Scheme 2. Synthesis of the *E*-*N'*-alkenylureidonitrile starting material.

Table 1. Reaction conditions for *E*-alkenylation.



entry	base[a]	additive	time, T	**3a** *E*:*Z*[b]	**4a**/%[c] (*E*:*Z*)[b]	**5**/%[c,d]
1	KHMDS	–	3 h, -78 °C	94:6	17 (66:34)	50
2	KHMDS[e]	–	1 h, 0 °C	94:6	75 (>95:5)	5
3	*sec*-BuLi	–	2 h, -78 °C	>95:5	46[f] (>95:5)	0[g]
4	*sec*-BuLi	DMPU[h]	2 h, -60 °C	>95:5	93 (>95:5)	0[g]

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5	KHMDS[e]	–	1 h, 0 °C	74:26	73 (85:15)	5
6	*sec*-BuLi	DMPU[h]	2 h, -60 °C	74:26	89 (80:20)	0[g]

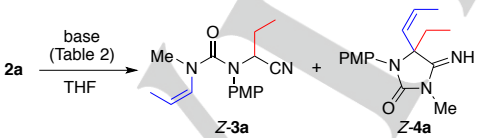
[a]KHMDS = potassium hexamethyldisilazide (2.5 equiv; 1.0 M in THF); *sec*-BuLi (2.1 equiv; 1.4 M in cyclohexane) added to **3a** in THF. [b]By ^{1}H NMR. [c] [c] Isolated yield. [d]**5** isolated as a single diastereoisomer. [e]Inverse addition; [f]**3a** recovered (51%), *E*:*Z* >95:5; [g]Undetectable in ^{1}H NMR spectrum of crude reaction mixture; [h]DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, 10% by volume.

KHMDS at –78 °C was evidently basic enough to form a metallated nitrile **3aM**:[13,14] the principal product of the reaction of **3a** was **5** (entry 1), which results from anionic cyclisation[11,15] of **3aM** onto the alkene. Nonetheless, a small amount of a *C*-alkenylated product **4a** was formed, the yield of which increased significantly on raising the temperature to 0 °C (entry 2). Iminohydantoin **4a** results from migration of the *N*-alkenyl function to the α-carbon of the aminonitrile, followed by cyclisation of the resulting ureide anion onto the nitrile function (see Scheme 6 for a detailed mechanistic discussion). To minimise formation of cyclisation product **5**, the base was changed to *sec*-BuLi[10b] with the aim of eliminating the proton source from the reaction mixture (entry 3). Raising the temperature to –60 °C and further activating the intermediate lithionitrile by adding the solvating agent DMPU[11,16] returned an excellent yield of the *C*-alkenylated product **4a** (entry 4).

With both bases, at the higher temperatures (entries 2, 4), **4a** was formed with complete *E* selectivity. Nonetheless, the formation of some *Z*-**4a** in entry 1 suggested that *Z* products might be formed under certain conditions from *Z* alkenyl urea starting materials. Indeed, repeating the reactions with both KHMDS and *sec*-BuLi using samples of **3a** containing 26% of its *Z* isomer gave a significant proportion of the *Z* isomer of **4a** (entries 5, 6) suggesting that the alkene migration may be stereospecific.

To explore this possibility further necessitated a *Z*-selective synthesis of the alkenylurea starting materials. *N*-Allyllithium derivatives of amides, carbamates and ureas adopt a *Z* configuration to facilitate interaction between the Li cation and the carbonyl donor.[13,17] Accordingly, the geometry of products obtained from lithiation and reprotonation of *N*-allyl ureidonitrile **2a** was explored (Table 2).

Table 2. Reaction conditions for *Z*-alkenylation.

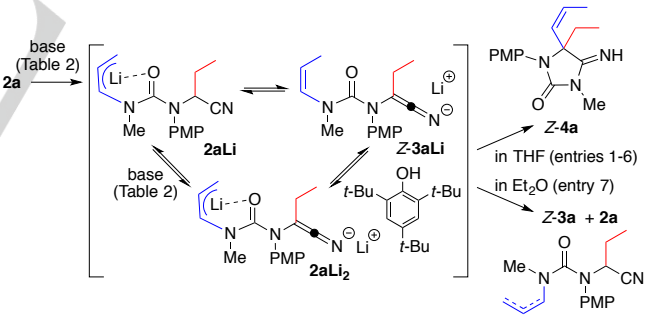


Z-**3a** *Z*-**4a**

entry	base[a]	time, T	**2a**[b] /%	*Z*-**3a**[c] /%	*Z*-**4a**[c] /%
1[d]	*sec*-BuLi	2 h, -60 °C	0[e]	0[e]	0[e]
2	*sec*-BuLi	2 h, -78 °C	7	7	56
3	*sec*-BuLi[f]	1 h, -78 °C	14	0[e]	56
4	LDA	5 h, -78 °C	3	9	56
5[g]	*sec*-BuLi	2 h, -78 °C	11	0[e]	62
6[h]	*sec*-BuLi	2 h, -78 °C	0[e]	0[e]	65
7	*sec*-BuLi[i]	2 h, -78 °C	27	53	0[e]

[a]2.1 equiv in THF unless otherwise stated. [b]Recovered starting material. [c]>95:5 *Z* by NMR of crude reaction mixture. [d] DMPU added, 10% by volume in THF. [e]Undetectable in ^{1}H NMR spectrum of crude reaction mixture. [f]1.0 equiv. [g]Quenched by dropwise addition of 2,4,6-tri-*tert*-butylphenol (2.2 equiv). [h]2,4,6-tri-*tert*-butylphenol (1.0 equiv) added dropwise after 30 min; methanol (excess) added after 1.5 h. [i]Reaction carried out in Et_2O.

The optimised conditions of Table 1 (*sec*-BuLi in 10:1 THF:DMPU at –60 °C) led to decomposition of **2a** (Table 2, entry 1). However, with *sec*-BuLi at a lower temperature and in the absence of DMPU, *Z*-**4a** was formed as a single geometrical isomer (entry 2).. No significant difference in reaction outcome was observed with only 1 equiv of base (entry 3), so we assume that the pK_a of proposed lithiated intermediates **2aLi** and **3aLi** (Scheme 3) must be similar enough to allow the alkene migration to occur from an equilibrium of these two anions. Using LDA to facilitate the necessary proton transfers gave little change in the reaction outcome (entry 4), but γ-reprotonation of **2aLi$_2$** using 2,4,6-tri-*tert*-butylphenol as a bulky proton source showed a slight improvement in the yield of *Z*-**4a** (entry 5). Optimally, deprotonation **2a** at –78 °C with 2.1 equiv. *sec*-BuLi followed by the slow addition of 1 equiv of the phenol allowed full conversion to a single geometrical isomer of the product *Z*-**4a** in 65% yield (entry 6). *Z*-**4a** is formed by a remarkable one-pot sequence of *Z*-stereoselective alkene isomerisation, geometry retentive *C*-alkenylation, and iminohydantoin cyclisation of **2a**. Replacement of THF by Et_2O interrupted the alkenyl shift (entry 7). Scheme 3 summarises the proposed deprotonation/reprotonation pathways leading from **2a** to **4a**.

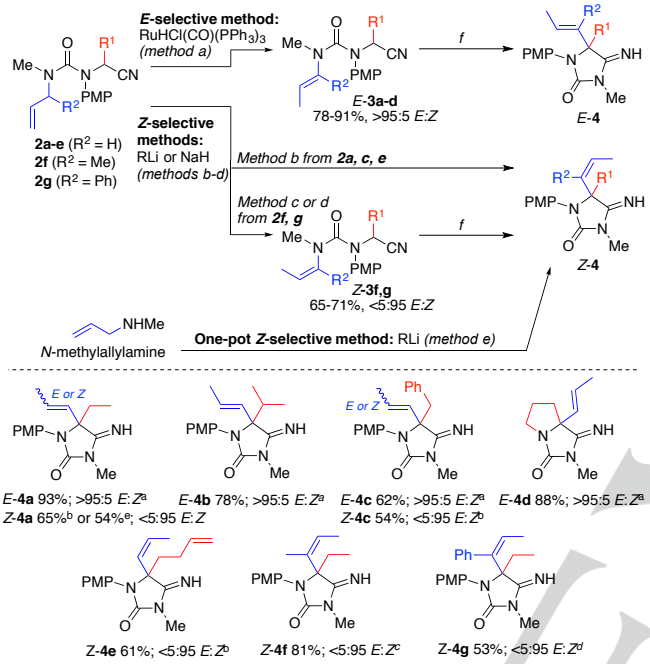


Scheme 3. One-pot stereoselective *Z*-olefin isomerisation, geometry retentive alkenylation and cyclisation.

Combining the results of Tables 1 and 2 allowed us to make a range of amino-acid-derived *E*- or *Z*-alkenyl iminohydantoins **4a-g** carrying a range of side chains R^1 by the stereodivergent strategy illustrated in Scheme 4. From allyl ureas **2**, Ru chemistry[12,13] gave *E* products and allyllithium chemistry[13,17] gave *Z* products. Derivatives bearing linear alkyl substituents such as **2a** and **2d** gave 5-alkenylated iminohydantoins *E*-**4a**, *Z*-**4a** and *Z*-**4e** in good yield. Bulkier α- and β-branched substituents were also tolerated in valine derivative *E*-**4b** and phenylalanine derivatives *E*- and *Z*-**4c**. α-Alkenyl proline-derived *E*-**4f** (which of course lacks the *p*-methoxyphenyl *N*-protecting group) was obtained in 88% yield as a single isomer. The reaction sequence leading to *Z*-**4a** was telescoped even further

to a one-pot process in which *N*-allyl urea **2a** forms under the same basic reaction conditions as the alkenyl isomerisation and migration (method e).[18]

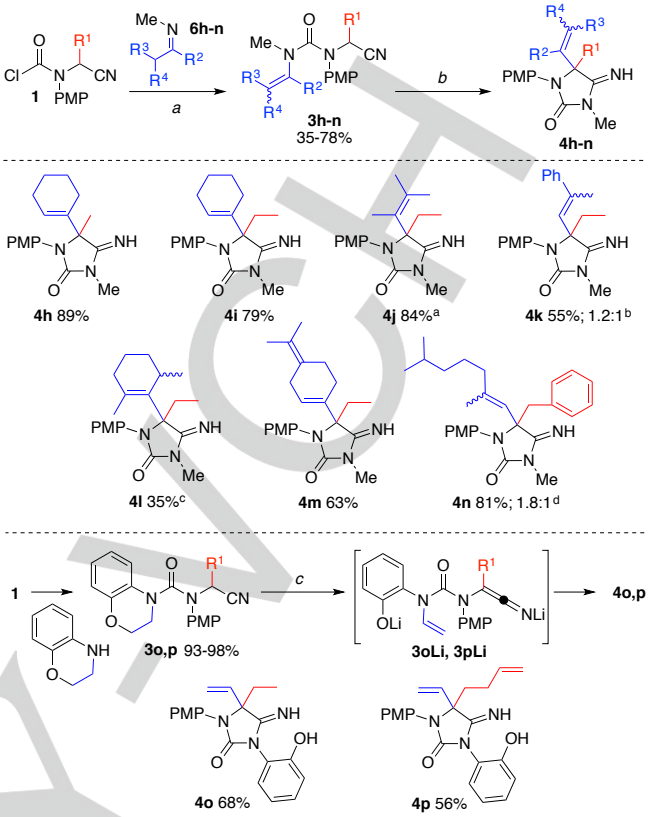
Steric hindrance at the α-position means that *N*-allyllithiums bearing substituents α to N are protonated to yield *Z*-alkenylureas with complete regioselectivity.[13,17] Thus the trisubstituted *Z*-alkenes **4f** (R^2=Me) and **4g** (R^2=Ph) were formed in good yields from **2f** and **2g** by treating firstly under basic conditions that avoid alkenyl migration (*sec*-BuLi in Et_2O or NaH in DMF), and then with *sec*-BuLi in 10:1 THF:DMPU at –60 °C.



[a]Method a: $RuHCl(CO)(PPh_3)_3$ (5 mol%), THF, 70 °C, 16 h; [b]Method b: (i) *sec*-BuLi (2.1 equiv), THF, -78 °C, 30 min.; (ii) *t*-$Bu_3C_6H_2OH$ (1 equiv), THF, 1.5 h; [c]Method c: (i) *sec*-BuLi (2.1 equiv), Et_2O, -78 °C, 30 min.; (ii) *t*-$Bu_3C_6H_2OH$ (2.1 equiv), Et_2O, 5 min [d]Method d: NaH (1.2 equiv), DMF, rt, 3 h; [e]Method e from *N*-methylallylamine: (i) n-BuLi (1 equiv); (ii) 1a, THF, rt, 16 h; (iii) *sec*-BuLi (2.1 equiv), THF, -78 °C, 30 min.; (iv) *t*-$Bu_3C_6H_2OH$ (1.1 equiv), THF, 2 h. Method f: *sec*-BuLi (2.1 equiv), THF, DMPU (10:1), –60 °C, 2-3 h.

Scheme 4. Stereodivergent alkenylation

Alternative routes to the starting *N*-alkenyl ureas[13,19] allowed a range of amino nitrile ureas bearing differently substituted alkenes, **3h-n**, to be prepared from imines **6h-n** (Scheme 5). *N*-Alkenylureas **3h-n** were treated with *sec*-BuLi in THF and DMPU to yield **4h-n**. The *in situ* generation of *N'*-vinyl ureas from **3o,p** by base-mediated ring-opening of morpholine followed by alkene migration[19a] gave *C*-vinyl products **4o** and **4p**. Cyclic and acyclic tri- and even tetra-substituted olefin products **4h-k** were obtained in good yields, though yields dropped for the bulky cyclic alkene product **4l**. Transfer of complex cyclic and acyclic natural-terpene-like alkenes gave products such as **4m** (derived from terpinolene) and **4n** (derived from 2H-citral).

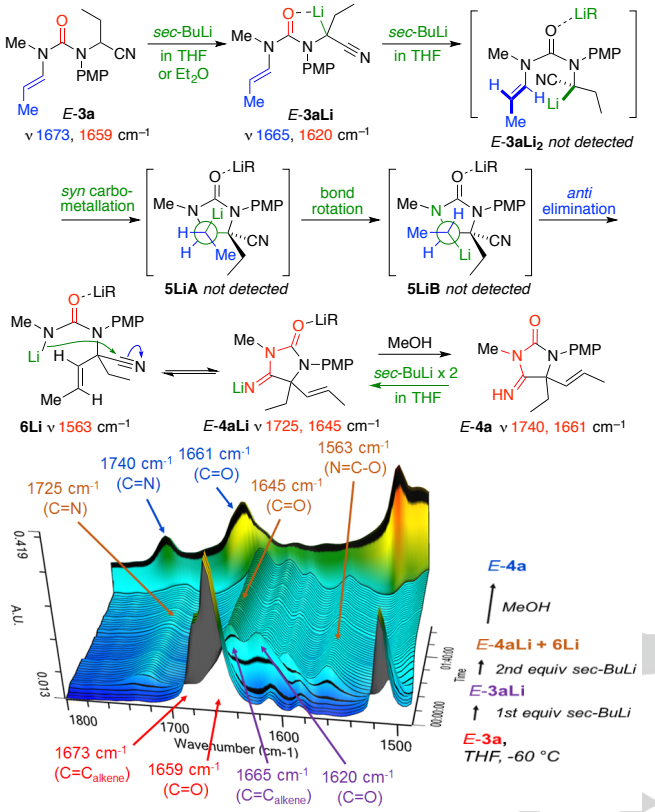


Methods: *a* 2,6-lutidine, microwave, KI, CH_3CN, 110-140 °C, 2-4 h; *b* *sec*-BuLi (2.1 equiv); THF, DMPU (10:1), –60 °C, 1-16 h; *c* *sec*-BuLi (3 equiv); THF, DMPU (10:1), –60 °C, 3 h [a]After 6 h at –40 °C; [b]As a 1.2:1 *E:Z* isomeric mixture from 3k (*E:Z* = 1.8:1); configuration determined by NOE; [c]4l obtained after 16 h at –20 °C as a single diastereoisomer; relative configuration not determined; [d]As a 1.8:1 *E:Z* isomeric mixture from 3n (*E:Z* = 2.5:1); alkene configuration determined by NOE.

Scheme 5. Hydantoins from *N'*-alkenyl-*N*-ureidonitriles

Formally, the alkenyl migration is a stereoretentive nucleophilic substitution at a carbon sp^2 centre.[20] To elucidate further mechanistic details of this unusual transformation, the rearrangement of *E*-**3a** was followed by *in situ* IR spectroscopy (React-IR) (Scheme 6).[21] The experiments were carried out without DMPU in order to avoid obscuring the carbonyl region of the spectrum. In THF at –60 °C, *E*-**3a** shows two absorptions at 1673 and 1659 cm^{-1} which disappear over a period of 5 min on treatment with 1 equivalent of *sec*-BuLi, being replaced by two absorptions at 1665 and 1620 cm^{-1}. The same spectrum is generated by treating *E*-**3a** with *sec*-BuLi in Et_2O at –78 °C, conditions under which no migration of the alkenyl group takes place, so we assign these new absorptions to lithionitrile intermediate *E*-**3aLi**. A second equivalent of *sec*-BuLi in THF leads immediately to the appearance of new IR absorptions. One appears at 1563 cm^{-1}, which we assign to **6Li** by analogy with previously similar reported intermediates,[11] and two more absorptions appear at 1725 and 1645 cm^{-1} corresponding to *E*-**4aLi. 6Li** and *E*-**4aLi** may coexist as an equilibrium, which is driven to product *E*-**4a** upon quench with MeOH at –60 °C. The identity of *E*-**4aLi** was confirmed by deprotonation of product *E*-**4a** (see supporting information for details). The necessity for two

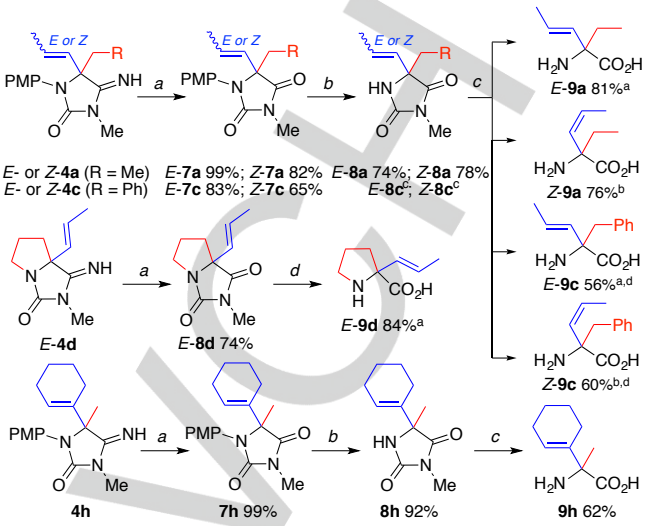
equivalents of alkyllithium to promote the migration suggests a role for the alkyllithium in coordinating the urea carbonyl and assisting the conformational change from **3aLi** to **3aLi$_2$**[10e,f] that is necessary for the reacting substituents to approach one another.



Scheme 6. Intermediates in the rearrangement of *E*-**3a** identified by ReactIR. For clarity, solvation/aggregation of metallated species is not shown.

The formation of imidazolidinone **5** with KHMDS as base (Scheme 2) suggested the possible intermediacy of a structure such as **5Li**, but (as with most cases of the related aryl migrations[10a,e]) we were unable to identify absorptions corresponding to such a cyclic intermediate. Nonetheless, the geometry-retentive stereospecificity of the reaction suggests that the detailed pathway of the alkenyl migration may involve the addition-elimination reaction shown in Scheme 6, in which *syn*-carbometallation[22] to give **5LiA** is followed *anti* elimination from conformer **5LiB**.

Both the 5,5-disubstituted hydantoin and ring-opened *C*α-disubstituted amino acid derivatives of iminohydantoins **4** are of biological interest.[1-5] The conversion of *E*- and *Z*-**4** into these targets, with preservation of the double bond geometry, was achieved by acidic hydrolysis of each of *E*- and *Z*-**4a,c** to give the corresponding hydantoins *E*- and *Z*-**7a,c** (Scheme 7). Oxidative removal of the *p*-methoxyphenyl group gave hydantoins *E*- and *Z*-**8**, which are unsaturated analogues of biologically active hydantoins (e.g. mephenytoin, phenytoin).[5a-b] *E*-**4d** likewise hydroysed in acid to give hydantoin *E*-**8d**. Treatment of **8** with refluxing sodium hydroxide gave quaternary α-alkenyl amino acids **9**. No alkene isomerisation was detected during the cleavage of **4** to **9**. Thus, the route from **2** to **9**, via **4**, constitutes a divergent *E* or *Z*-stereoselective method for the *C*-alkenylation of natural and unnatural amino acids.



[a]>95:5 *E*:*Z* by NMR; [b]<5:95 *E*:*Z* by NMR; [c]Not isolated; [d]Yield over two steps from 7c. Methods (a) HCl (2 M, aq.)/MeOH 1:1, reflux, 48-72 h; (b) CAN (4 equiv), CH_3CN/H_2O 2:1, 0 °C, 5 min; (c) NaOH (4 M, aq.), reflux, 48 h; (d) NaOH (4 M, aq.)/1,4-dioxane 1:1, reflux, 72 h.

Scheme 7. Conversion of products into hydantoins 8 and quaternary α-alkenyl amino acids **9**.

In summary, this general, direct *C*-alkenylation of tertiary amino nitriles allows the connective synthesis of alkenylated hydantoins. The method is sterodivergent, providing either the *E* of the *Z* isomer of the product from the same starting materials, themselves available by simple Strecker and acylation chemistry. Quaternary α-alkenyl amino acids are formed as single *E* or *Z* isomers upon cleavage of the hydantoin products.

Acknowledgements

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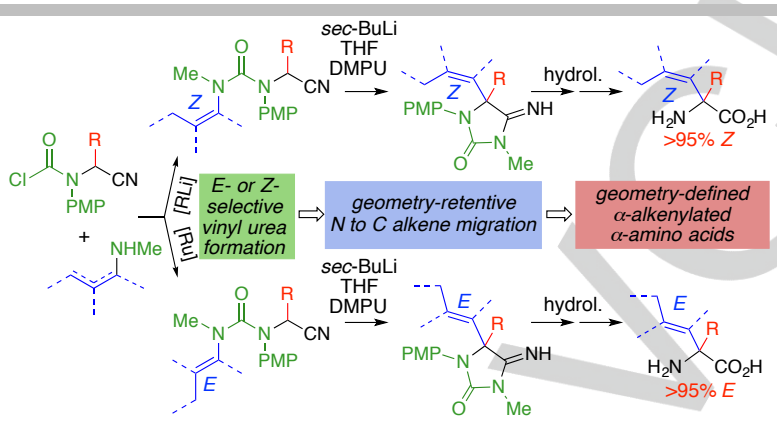
COMMUNICATION

E- or *Z*-alkenylurea derivatives of aminonitriles undergo stereospecific N to C alkenyl migration on treatment with base, forming alkenyl hydantoins or (on hydrolysis) alkenyl amino acids of biological and pharmaceutical



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