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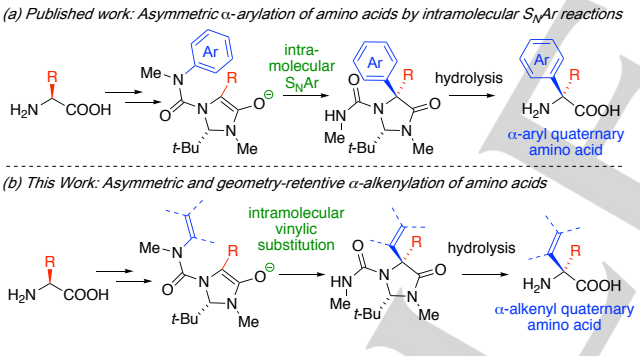
Asymmetric and Geometry-selective α-Alkenylation of α-Amino Acids

Hossay Abas, Josep Mas-Roselló, Mostafa Mahmoud Amer, Derek J. Durand, Robin R. Groleau, Natalie Fey, Jonathan Clayden*

Abstract: Both *E*- and *Z*-N'-alkenyl urea derivatives of imidazolidinones may be formed selectively from enantiopure α-amino acids. Generation of their enolate derivatives in the presence of K^+ and 18-crown-6 induces intramolecular migration of the alkenyl group from N' to Cα with retention of double bond geometry. DFT calculations indicate a partially concerted substitution mechanism. Hydrolysis of the enantiopure products under acid conditions reveals quaternary α-alkenyl amino acids with stereodivergent control of both absolute configuration and double bond geometry.

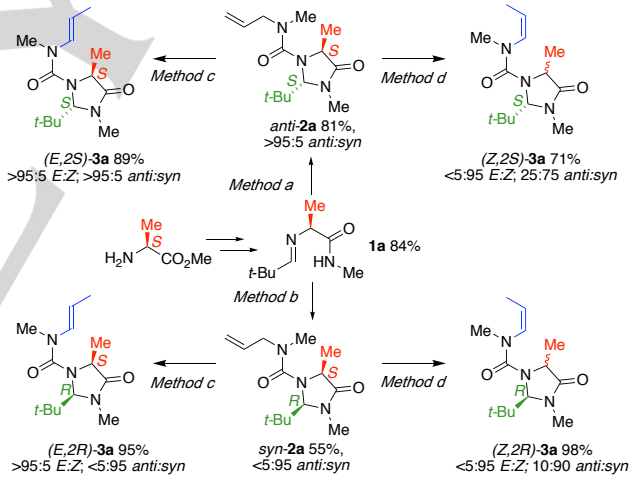
Introducing a fourth substituent to the α-carbon of amino acids confers valuable structural and functional properties on their derivatives.[1] These quaternary amino acid residues promote helical structures and increase the proteolytic stability of peptides and proteins.[2] While there are many methods for the α-alkylation of amino acids, the introduction of unsaturated (sp^2) substituents at this position has proved more challenging synthetically.[3] α-Alkenyl α-amino acids are nonetheless themselves an important class of structures, displaying a wide range of biological activities such as inhibition of decarboxylase enzymes,[4,5] or antibiotic[6] and anticarcinogen[7] activity.



Scheme 1. Arylation and alkenylation of amino acid derivatives by *N'* → *C* migration across a urea tether.

Existing synthetic approaches to enantiopure α-alkenylated amino acid derivatives rely on multi-step reaction sequences,[8–12] typically requiring the introduction of a functionalised chain (such as an alcohol or an alkyl selenoxide) at the α position,[13–15] the use of activated acetylene electrophiles,[16–18] or [2,3]-sigmatropic rearrangements of allylic amines.[19] We recently reported[3] a direct and general synthesis of enantiomerically enriched α-arylated quaternary amino acids by combining the electronically versatile intramolecular SNAr chemistry characteristic of N-aryl ureas[20,21] with Seebach's 'self-regeneration of stereocenters' methodology (Scheme 1a).[22] We have found that *N'*-alkenyl groups likewise migrate from N' to C within anionic derivatives of ureas,[23,24] and we now report a practical method for the α-functionalisation of amino acids with alkenyl substituents (Scheme 1b) in which both the absolute configuration of the stereogenic centre and geometric configuration of the double bond are controlled.

N'-Alkenylureas **3** may be made by isomerization of their *N'*-allyl congeners,[25] so we began by preparing *N'*-allylureido imidazolidinones **2** (Scheme 2) from L-alanine. Either the *syn* or the *anti* diastereoisomer of **2a** could be made selectively from a common imine intermediate **1a** by choice of conditions, with acylation of the imine with a carbamoyl chloride at elevated temperatures giving *syn*-**2a**,[3] and *anti*-**2a** being obtained by acylating *N*-methylallylamine with the *anti* carbamoyl chloride generated using phosgene and pyridine.[26]



Scheme 2. Stereodivergent formation of N'-alkenylureido imidazolidinones.

Method a: 1. $COCl_2$ (1.5 equiv) THF, 2 h, rt; 2. pyridine (2 equiv), 16 h, rt. 2. *N'*-Me-*N'*-allyl amine (1.1 equiv), Et_3N (1.2 equiv), MeCN, rt. 2-16 h. *Method b:* 1. *N'*-Me-*N'*-allylcarbamoyl chloride (1.2 equiv), DMAP (5 mol%), 1,2-DCE (1,2-dichloroethane), reflux, 4 d. *Method c:* $RuHClCO(PPh_3)_3$ (5 mol%), THF, 70 °C, 16 h. *Method d:* 1. LDA (3 equiv), THF, –78 °C, 1 h; 2. $(t\text{-Bu})_3C_6H_2OH$ (3 equiv).

The *N*-allyl ureas **2** were isomerized to the *E*-alkenyl ureas *E*-**3** with a Ru catalyst and to *Z*-alkenyl ureas *Z*-**3** by γ reprotonation of the *Z*-configured allyllithium derivative of **2** with a bulky proton source (Scheme 2).[24,27] These methods allowed the stereodivergent formation of four stereoisomers of **3a** as starting materials for alkenyl migration having either *2R* or *2S* configuration at the *tert*-butyl-bearing centre and either *E* or *Z* double bond geometry.

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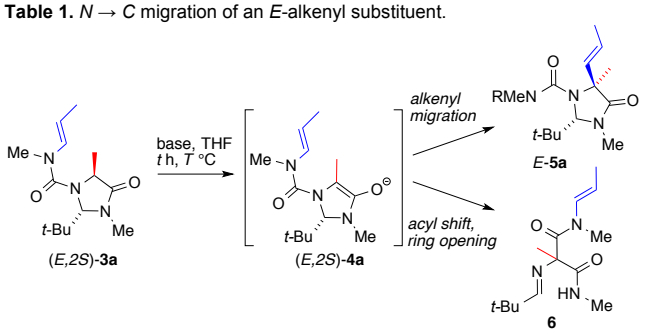
Table 1. *N* → *C* migration of an *E*-alkenyl substituent.



Entry	Base[a]	Additive	*t*, *T*	Recovered *E*-**3a** [%][b]	Yield *E*-**5a** [%][b,c]	Yield **6** [%][b]
1	LDA	–	2 h, 0 °C	–	–	50[d]
2	KHMDS	–	2 h, 0 °C	>95[e]	–	–
3	KHMDS	–	4 h, 20 °C	–	38	30
4	KHMDS	18-c-6[f,g]	0.5 h, 0 °C	–	60, 54[h]	–
5	KHMDS	18-c-6[f,i]	4 h, 0 °C	–	75[h], 84[h,i,j]	–

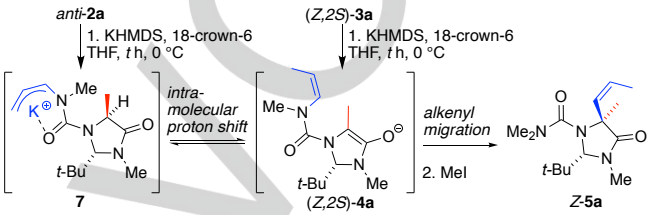
[a] LDA = lithium diisopropylamide (2 equiv; 0.6 M in THF) added to **3a** in THF, or **3a** in THF added to KHMDS = potassium hexamethyldisilazide (2 equiv; 1.0 M in THF). [b] Yield determined by ^{1}H NMR using hexamethylbenzene as internal standard except entry 5. [c] >95:5 *E*:*Z*; >95:5 *dr*. R = H except entry 5. [d] Also formed in 83% yield in presence of DMPU. [e] *Anti* diastereoisomer. [f] 18-c-6 added as a 1 M solution in THF. [g] 10 equiv. [h] Isolated yield. [i] 2.2 equiv. [j] MeI added after 4 h at 0 °C; R = Me.

The N → C migration of the alkenyl groups of **3** was explored using (*E*,*2S*)-**3a** (Table 1). Treatment with LDA gave an enolate **4a**, but at 0 °C this enolate underwent 1,2-acyl transfer of the carbamoyl group followed by ring opening give the imine **6** (entry 1). KHMDS promotes aryl migration to enolates,[3] but was insufficiently basic to deprotonate the starting material at 0 °C (entry 2). At 20 °C KHMDS delivered a single diastereoisomer of **5a**, still accompanied by 30% of the unwanted acyl migration product **6** (entry 3). The key to selective migration turned out to be 18-crown-6 (18-c-6), which disfavoured the unwanted formation of **6**: KHMDS with 10 equiv 18-c-6 gave **5a** in 60% yield after 30 min (entry 4), rising to 75% yield after 4 h with 2.2 equiv 18-c-6 (entry 5). Purification of the product (and eventual conversion to the free amino acid) was simplified by quenching the product with methyl iodide, which gave the rearranged *N*,*N*-dimethylurea *E*-**5a** (R = Me) in 84% yield. The product *E*-**5a** (R = Me) was formed as a single (*E*,*S*,*S*) diastereoisomer, with migration of the alkenyl group to the less hindered face of the imidazolidinone and retention of *E* double bond geometry.

These optimal conditions were applied to the *Z*-isomer (Table 2, entry 1) using a mixture of (*Z,2S*)-**3a** (Scheme 1) epimeric at the α-stereocentre, but configurationally uniform at the *tert*-butyl-bearing centre. Migration of the Z alkene was successful, giving a single diastereoisomer of *Z*-**5a** in 70% yield (the migration is diastereoselective) and, remarkably, as a single *Z*-geometrical isomer (the migration is geometrically stereospecific).

Strong base promotes both the isomerisation of the *N*-allylurea starting material to the *Z* alkene and the subsequent migration step, so a three-step, one-pot transformation of *anti*-**2a** to **5a** was explored. Under the optimized migrating conditions (Table 2, entry 2), *N*-allyl imidazolidinone **2a** gave 66% of the desired product **5a**, but with a *Z*:*E* ratio of 85:15 ratio. 0.5 Equiv KHMDS gave only 34% of **5a**, but with >95:5 *Z*:*E* selectivity (entry 3). We propose that this selectivity arises because an allyl anion **7** is formed that may be reprotonated either by an intramolecular *Z*-selective 1,7-proton transfer shift, or by a geometrically unselective intermolecular proton transfer from hexamethyldisilazane. Following this rationale, we added 1 equiv. KHMDS slowly over 30 mins to limit the amount of disilazane in the reaction mixture and hence favour selective intermolecular proton transfer (entry 4). These conditions gave 63% of the *Z*-migrated product, with only trace amounts of the *E* isomer (94:6 *Z*:*E*).

Table 2. *N* → *C* migration of a *Z*-alkenyl substituent.



Entry	SM	equiv KHMDS[a]	*t*	yield **5a** [%][b]	*Z*:*E*[c]
1	**3a**	2	4 h	70	>95:5
2	**2a**	2	4 h	66	85:15
3	**2a**	0.5	1 h	34[d]	>95:5
4	**2a**	1[e]	1 h	63	94:6

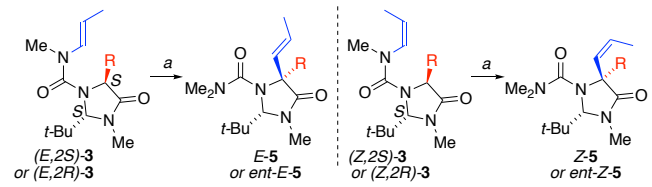
[a] KHMDS added to substrate + 3 equiv. 18-crown-6 in THF over 5 mins unless otherwise stated. [b] Isolated yield. [c] From ^{1}H NMR of crude reaction mixture. [d] 55% unreacted starting material recovered. [e] KHMDS added over 30 mins.

The alkenylation was explored with a range of natural and non-natural amino acids (Scheme 3). All four possible isomers of L-alanine derived ureido imidazolidinone **5a** were made with retention of the double bond geometry. A further range of imidazolidinones derived from amino acids bearing alkyl (**5b**), arylalkyl (**5c**), unsaturated (**5d**), benzylic (**5e**) and branched (**5f**) side chains likewise rearranged successfully, giving consistently high yields of the *Z* substituted products in which the alkene has migrated *anti* to the *tert*-butyl group. Notably, the bulky leucine-derived imidazolidone (*Z,2S*)-**3f** was *Z*-alkenylated to give *Z*-**5f** in 77% with complete diastereocontrol, and an X-ray crystal structure[28] of the product confirmed its stereochemistry. Functionalised side chains were tolerated, with *Z*-alkenylated derivatives of L-methionine *Z*-**5g**, *Z*- L-Tyr **5h**, *Z*- L-dopa **5i**, and *Z*- L-Trp derivatives **5k** all forming with high yield, excellent *dr* and full *Z* selectivity.

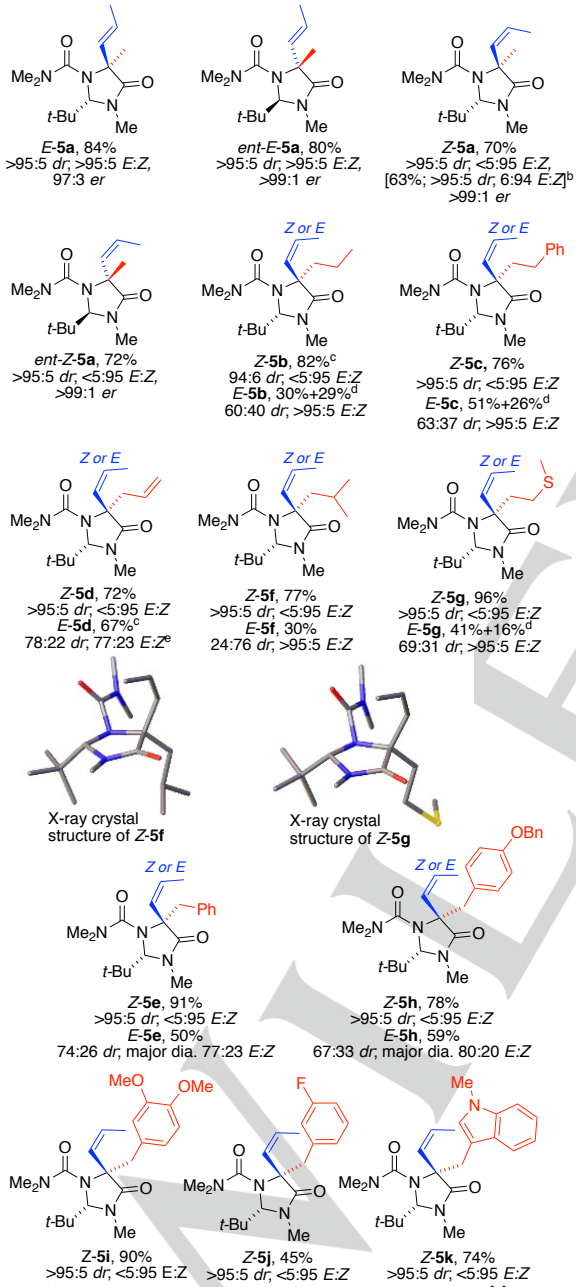
The *E*-isomers *E*-**5b**-**5i** were obtained in moderate to good yields, with the exception of the hindered L-Leu-derived imidazolidinone *E*-**5f**. Non-aromatic substrates displayed excellent retention of the *E* double bond geometry during the migration, but Phe and its congeners displayed lower selectivity. In contrast to the *Z* isomers, the diastereoselectivity of the rearrangement depended on the steric bulk of the amino acid side chain, dropping from >95:5 dr with alanine-derived *E*-**5a** to 74:26 dr for *E*-**5e** and 60:40 dr for *E*-**5b**. With leucine-derived *E*-**5f**, the major product became the diastereoisomer with the alkenyl group *cis* to the bulky *tert*-butyl group. We assume that

10.1002/anie.201813984

the less sterically demanding *E* alkenyl groups favour a geometry where the amino acid side chain, especially if hindered (i.e. R > Me) competes for the *anti* relationship with the *tert*-butyl group.



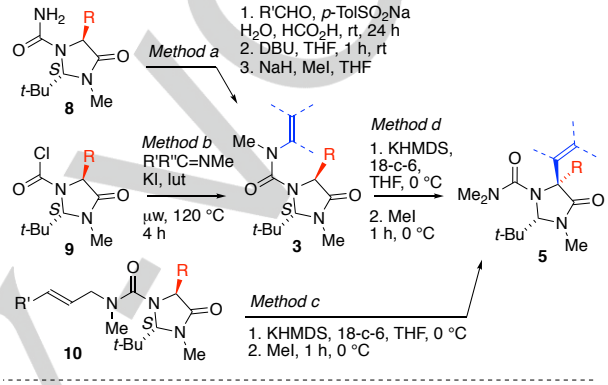
Conditions *a*: 1. KHMDS (2 equiv), 18-crown-6 (2.2 equiv), THF, 0 °C; 2. MeI, 1 h, 0 °C

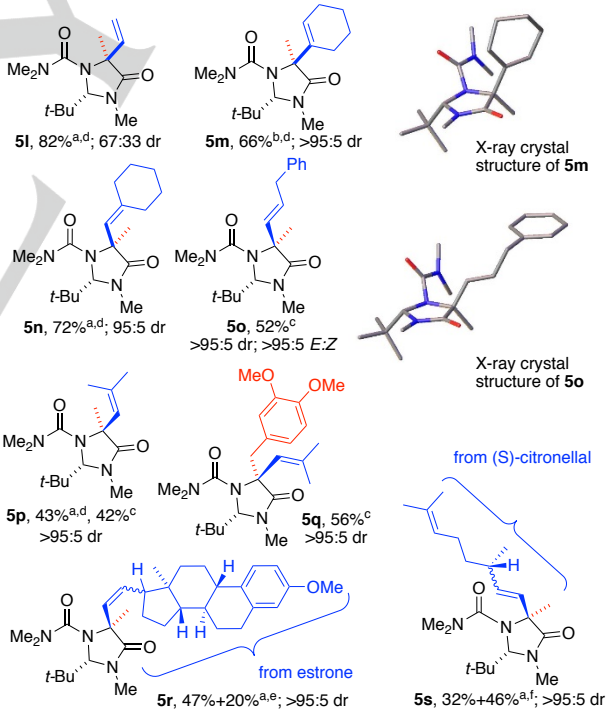


Scheme 3. Asymmetric stereodivergent alkenylation[a]

[a] Yields and selectivities by conditions *a* unless otherwise indicated. [b] By one-pot isomerisation-migration method: 1. 18-c-6 (2.2 equiv), KHMDS (1-3 equiv), THF, 0 °C; 2. MeI, 1 h, 0 °C. [c] Isolated yield of pure major (*S,S*)-diastereoisomer. [d] Isolated yields of major and minor diastereoisomers respectively. [e] Starting from (*2S*)-**3d** as an 85:15 *E:Z* mixture.

This observation led us to expect that more bulky alkenes would migrate more diastereoselectively, so we looked to expand the scope of the *N*-alkenylureas that undergo the rearrangement. Three methods for the synthesis of *N*-alkenylureas,[24,25] are shown in Scheme 4: starting materials **3** lacking a 1-substituent were most readily prepared by the sulfinate-promoted condensation of the urea **8** with an aldehyde (Method a).[29,30] This method failed with ketones, so 1,1-disubstituted alkenes (eg **3m**) were instead made by acylation of an *N*-methyl ketimine with the carbamoyl chloride **9**. Alternatively, the one-pot method from Scheme 2 allowed access to complex variants directly from their *N*-allyl isomers.[31]





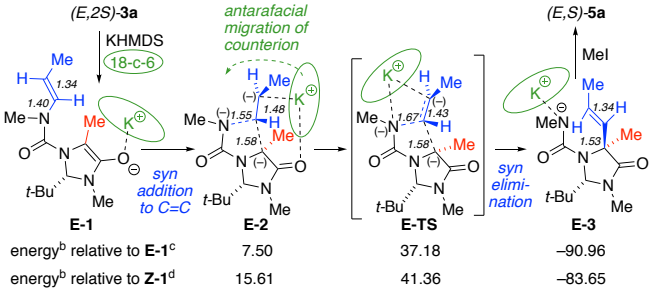
Scheme 4. *N* → *C* alkenylation with a range of alkenes

[a] Starting material **3** by Method a; [b] Starting material **3** by method b; [c] By method c; [d] By method d. [e] Isolated *E* and *Z* isomers from a 75:25 *E:Z* mixture of starting materials. [f] Isolated *E* and *Z* isomers from a 40:60 *E:Z* *E:Z* mixture of starting materials.

Scheme 4 shows the results of migrating these substituted alkenes. Mono-, di- and tri-substituted alkene products **5l-q** were obtained in moderate to high yields, with complete geometrical fidelity and (with the exception of the simple vinylated product **5l**)

with complete diastereoselectivity. The steroid-derived **3r** and the terpene-derived **3s** rearranged stereospecifically (the product ratio matched the starting material ratio) to give the unusual 'hybrid' steroid amino acid derivative **5r** and the terpenoid amino acid derivative **5s**.

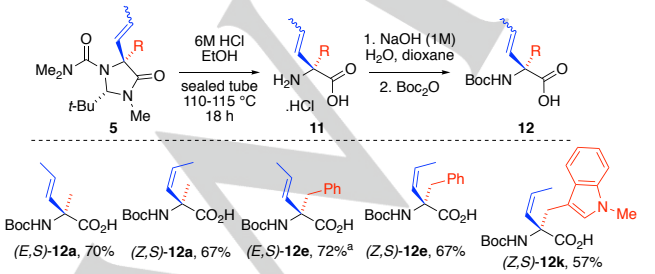
The detailed mechanism of the reaction is intriguing. The migrating alkenes are electron-rich *N*-acylenamines typically unsusceptible to attack by nucleophiles. A similar lack of requirement for electron-deficient activating groups was noted in the corresponding arylation reactions,[3] where a conformational preference for the nucleophilic enolate to lie very close to the aromatic ring seems to underlie the reactivity.



Scheme 5. Mechanism considered computationally.[a]

[a] Calculated bond lengths given in Å. [b] Calculated relative Gibbs free energies in kJ mol^{-1} [B3LYP-D3, 6-31+G(d), LACV3P on K, PCM (solvent=thf), 298 K]; [c] For reaction of *E*-**3a**; [d] For reaction of *Z*-**3a**.

We used standard DFT calculations (see SI for full computational details) to probe the mechanism of reaction of *E* and *Z*-**3a**, as set out [for (*E,2S*)-**3a**] in Scheme 5. After deprotonation, the charge on the enolate oxygen is stabilized by coordination to [K$^+$18-c-6] to give **E-1**. Development of the energetically accessible *syn*-carbometallation intermediate **E-2** is supported by chelation of the [K$^+$18-c-6] counterion. A transition state **E-TS** could be located that involved concerted shortening of the C-C bond between the alkenyl group and Cα (to 1.58 Å) and lengthening of the C-N bond (to 1.67 Å). **E-TS** can be reached by an effective inversion of planar configuration of the carbanion, either by antarafacial counterion migration involving a "windscreen wiper" motion of [K$^+$18-c-6], or by the approach of a second counterion (see SI). Rotation around the former double bond in the carbanionic intermediate, which would erode the selectivity, is prevented by steric interactions. Progression towards the migration product **E-3** by *syn*-elimination is then thermodynamically favorable, and results in retention of double bond geometry.



Scheme 6. Hydrolysis to protected quaternary amino acids.

[a] Starting material and product are 77:23 *E*:*Z*

Hydrolysis of the products **5** in acid[32] afforded the HCl salts of the amino acids without compromising the alkene geometry or enantiomeric purity (Scheme 6). Treatment with Boc_2O returned readily isolable *N*-protected α-alkenylated amino acids in good yields.

In summary, the enantioselective introduction of an alkenyl substituent to the α position of an amino acid is made possible by the diastereoselective rearrangement of an *N'*-alkenyl urea in which double bond geometry is reliably retained. Various stereoselective routes may be used to install the desired configurations in the starting material, and, provided certain conditions are met, the products are formed with excellent stereocontrol. Hydrolysis to valuable Cα quaternary alkenyl amino acids is possible by simple aqueous hydrolysis.

Acknowledgements

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Keywords: α-Alkenylation • Stereodivergent • Quaternary Amino Acids • Rearrangement • DFT

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[32] Raised temperatures (>150 °C) led to competing intramolecular hydroamination of the alkene, to give azetidine by-products.

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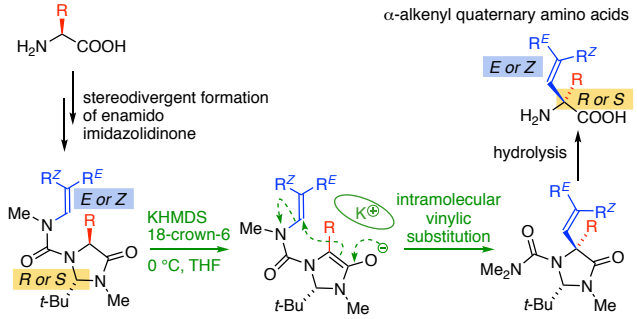

*Hossay Abas, Josep Mas-Roselló, Mostafa Mahmoud Amer, Derek J. Durand, Robin R. Groleau, Natalie Fey, Jonathan Clayden**

Page No. – Page No.

Asymmetric and Geometry-selective α-Alkenylation of α-Amino Acids

Both *E*- and *Z*-N'-alkenyl urea derivatives of imidazolidinones may be formed selectively from enantiopure α-amino acids. Generation of their enolate derivatives in the presence of K+ and 18-crown-6 induces intramolecular migration of the alkenyl group from N' to Cα with retention of double bond geometry. DFT calculations indicate a partially concerted substitution mechanism. Hydrolysis of the enantiopure products under acid conditions reveals quaternary α-alkenyl amino acids with stereodivergent control of both absolute configuration and double bond geometry.