



Cite this: *Green Chem.*, 2022, **24**, 7988

Received 3rd August 2022
 Accepted 23rd September 2022

DOI: 10.1039/d2gc02896d

rsc.li/greenchem

Base-selective access to highly functionalized heterocycles from multicomponent Ugi adducts†

Beatriz González-Saiz,^a Pablo Pertejo,^a Pablo Peña-Calleja,^a Marcin Mielczarek,^a Tomás Hermosilla,^a Israel Carreira-Barral,^a Olivia de Miguel,^a Francisco Rodríguez-Vidal,^b Roberto Quesada^a and María García-Valverde^{a*}

Selection of the appropriate base in Ugi/post-condensation sequences allows the selective syntheses of different ring-size functionalized lactams. The developed methodology uses inexpensive bases under mild and non-sensitive conditions leading to the facile generation of molecular diversity from simple synthons.

1. Introduction

The increasing demand for the development of new and efficient syntheses of N-heterocycles is explained mainly by their importance in the pharmaceutical and fine chemicals industries.¹ The synthesis of highly functionalized heterocycles remains a major challenge and continues to drive an intense research effort.² Different selective methodologies have been described, although many of them present drawbacks such as the need for expensive reagents, specific substrates, harsh or sensitive conditions or long synthetic sequences.³ Furthermore, some substitution patterns have not been described yet despite their promising applications as bioactive compounds or as intermediates in the synthesis of other compounds, mainly due to limitations of synthetic methodologies.⁴

The ring expansion of β -lactams is one of the various approaches to the synthesis of γ -lactam skeletons,⁵ favored due to the β -lactam ring strain.⁶ Single-step synthetic methodologies illustrating this reaction can be classified into three main categories: (a) intramolecular transamidation from the proper amino-substituted azetidinone, as 4-(1-aminoalkyl)⁷ or 3-(2-aminoalkyl)-2-azetidinone derivatives,⁸ which takes place through the $N1-C2$ cleavage and is the most common one, (b) the rearrangement favored by an electron-deficient position through the $C3-C4$ cleavage, as the expansion of 4-(1-haloalkyl)-2-azetidinones to γ -lactams *via* N -acyliminium intermediates,⁹ and (c) the rearrangement resulting from an

anionic position generated by strong bases, as the benzylic anions generated by LDA in N -benzyl-4-arylazetidinones which rearrange to a γ -lactam through a proposed imine anion intermediate originated in the $C4-N1$ cleavage.¹⁰ The examples within this latter methodology are very scarce,¹¹ probably due to the specificity of the substrates needed as well as the reaction conditions (LDA or n -BuLi in anhydrous THF) employed to achieve the expansion (Scheme 1a).

We envisaged the possibility of expanding the scope of this reaction to other substrates, and we planned to use Ugi/post-condensation sequences, seizing their huge potential to yield structurally complex molecules in expedited syntheses from a reduced number of steps.¹² Surprisingly, in addition to the applicability of this strategy to a broad spectrum of substrates, we have found that a rational design of β -lactams, selectively synthesized from Ugi adducts, enables the expansion to highly functionalized γ -lactams using weak bases, under mild and non-moisture-sensitive conditions (box in Scheme 1b). Thus, we have found that variation of the nature of the base employed leads to the selective synthesis of differently funcio-



Scheme 1 (a) Previous work on ring expansion of β -lactams through an anionic rearrangement and (b) summary of N-heterocycles synthesized from common Ugi adducts.

^aUniversidad de Burgos, Facultad de Ciencias, Burgos, Castilla y León, Spain

^bUniversidad de Burgos, Higher Polytechnic School, Av. Cantabria s/n, Burgos, Spain

†Electronic supplementary information (ESI) available. CCDC 2193426, 2193428–2193430 and 2193435. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2gc02896d>



nalized N-heterocyclic systems, some of them with unprecedented functionalization patterns, from common multicomponent Ugi adducts (Scheme 1b).

2. Results and discussion

2.1. Synthesis of azetidinones through Ugi/cyclization sequences

2.1.1. Synthesis of Ugi adducts. Initially, we decided to employ the methodology described for the synthesis of azetidinones through an Ugi/cyclization sequence¹³ implementing a crucial change for our purposes, the use of α -CH activated amines to favor their ulterior deprotonation.

In this way, we prepared different Ugi adducts **5** using 2-nitrobenzylamine **4a**, benzylamine **4b** and α -amino acid methyl esters **4c–g** as amines, along with chloroacetic acids **1a–b**, glyoxals **2a–f** and different isocyanides **3a–c** (Table 1). As we expected, in all cases the enol tautomer was the only one observed, but the spontaneous cyclization never took place.¹⁴

2.1.2. Synthesis of azetidinones from Ugi adducts. For the next stage, we observed that the cyclization to azetidinone strongly depended on several factors such as the substituents on the Ugi adduct coming from the halocarboxylic acid and the amine and the base employed. As this step was decisive for our purposes, we looked for the most general optimal conditions.

In this way, different bases were employed in order to achieve the selective cyclization of Ugi adduct **5a** to the corresponding azetidinone **6a**. Initially, we tried triethylamine under different conditions. It turned out that the use of three equivalents of this base in ethanol and ultrasonication for 1 hour afforded azetidinone **6a** with a moderate yield (entry 1, Table 2). Then, we tried potassium and sodium carbonates but the obtained yield was low, because the *O*-alkylation product was obtained along with the desired *C*-alkylation compound. Despite this result we observed the influence of cation size, as the smaller sodium cation favors *C*-alkylation¹⁵ (entry 2 vs. 4, Table 2). However, when cyclization with lithium carbonate was attempted, the Ugi adduct was recovered (entry 5, Table 2),

Table 1 Synthesis of Ugi adducts **5**



| Entry | 1 (R ¹) | 2 (R ²) | 3 (R ³) | 4 (R ⁴ , EWG) | 5 ^a (%) |
|-------|--|---|--|--|--------------------|
| 1 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5a (89) |
| 2 | 1a (H) | 2a (C ₆ H ₅) | 3b (CH ₂ C ₆ H ₅) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5b (67) |
| 3 | 1a (H) | 2a (C ₆ H ₅) | 3c (C(CH ₃) ₃) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5c (59) |
| 4 | 1a (H) | 2b (4-CH ₃ C ₆ H ₄) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5d (86) |
| 5 | 1a (H) | 2c (4-ClC ₆ H ₄) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5e (85) |
| 6 | 1a (H) | 2d (4-FC ₆ H ₄) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5f (86) |
| 7 | 1a (H) | 2e (4-CH ₃ OC ₆ H ₄) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5g (54) |
| 8 | 1a (H) | 2f (CH ₃) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5h (39) |
| 9 | 1b (C ₆ H ₅) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5i (93) |
| 10 | 1b (C ₆ H ₅) | 2d (4-FC ₆ H ₄) | 3a (cC ₆ H ₁₁) | 4a (H, 2-NO ₂ C ₆ H ₄) | 5j (86) |
| 11 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4b (H, C ₆ H ₅) | 5k (78) |
| 12 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4c (H, CO ₂ CH ₃) | 5l (52) |
| 13 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4d (C ₆ H ₅ , CO ₂ CH ₃) | 5m (70) |
| 14 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4e (CH ₃ , CO ₂ CH ₃) | 5n (65) |
| 15 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4f (CH ₂ C ₆ H ₅ , CO ₂ CH ₃) | 5o (55) |
| 16 | 1a (H) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4g (CH(CH ₃) ₂ , CO ₂ CH ₃) | 5p (78) |
| 17 | 1b (C ₆ H ₅) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4c (H, CO ₂ CH ₃) | 5q (83) |
| 18 | 1b (C ₆ H ₅) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4d (C ₆ H ₅ , CO ₂ CH ₃) | 5r (76) |
| 19 | 1b (C ₆ H ₅) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4e (CH ₃ , CO ₂ CH ₃) | 5s (81) |
| 20 | 1b (C ₆ H ₅) | 2a (C ₆ H ₅) | 3a (cC ₆ H ₁₁) | 4f (CH ₂ C ₆ H ₅ , CO ₂ CH ₃) | 5t (82) |

^a Yield after purification.



Table 2 Synthesis of β -lactams **6a–k** from Ugi adducts **5a–k**, all of them derived from benzyl amines, and X-Ray molecular structure of azetidinone **6a**. The ORTEP plot is at the 30% probability level

| Entry | 5 (R ¹ , R ² , R ³ , X) | Base | Equiv. | 6 ^a (%) | d.r. ^b |
|-------|---|--|--------|-----------------------------|------------------------|
| 1 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | NEt ₃ ^c | 3 | 6a (58) | — |
| 2 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | K ₂ CO ₃ ^d | 1.1 | 6a (14) ^f | — |
| 3 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | K ₂ CO ₃ ^d | 2 | 6a (—) ^g | — |
| 4 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | Na ₂ CO ₃ ^d | 1.1 | 6a (40) ^f | — |
| 5 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | Li ₂ CO ₃ ^d | 1.1 | 6a (—) ^h | — |
| 6 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiCl ^e | 1 : 10 | 6a (65) ^f | — |
| 7 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 10 | 6a (92) | — |
| 8 | 5a (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6a (88) ^f | — |
| 9 | 5b (H, C ₆ H ₅ , CH ₂ C ₆ H ₅ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6b (79) | — |
| 10 | 5c (H, C ₆ H ₅ , C(CH ₃) ₃ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6c (67) | — |
| 11 | 5d (H, 4-CH ₃ C ₆ H ₄ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6d (73) | — |
| 12 | 5e (H, 4-ClC ₆ H ₄ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6e (72) | — |
| 13 | 5f (H, 4-FC ₆ H ₄ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6f (68) | — |
| 14 | 5g (H, 4-CH ₃ OC ₆ H ₄ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6g (76) | — |
| 15 | 5h (H, CH ₃ , <i>c</i> C ₆ H ₁₁ , NO ₂) ^b | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6h (90) | — |
| 16 | 5i (C ₆ H ₅ , C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6i (84) | 24 : 76 ^{i,j} |
| 17 | 5i (C ₆ H ₅ , C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , NO ₂) | NEt ₃ ^c | 3 | 6i (93) | 87 : 13 ^{i,j} |
| 18 | 5j (C ₆ H ₅ , 4-FC ₆ H ₄ , <i>c</i> C ₆ H ₁₁ , NO ₂) | NEt ₃ ^c | 3 | 6j (86) | 86 : 14 ^{i,j} |
| 19 | 5k (H, C ₆ H ₅ , <i>c</i> C ₆ H ₁₁ , H) | CS ₂ CO ₃ /LiI ^e | 1 : 2 | 6k (87) | — |

^a Yield after purification. ^b Diastereomeric ratio determined by ¹H NMR. ^c In ethanol at room temperature and ultrasonication, 2 h. ^d In acetone at reflux, 12 h. ^e In acetonitrile at reflux, 12 h. ^f *O*-Alkylation by-product. ^g Mixture of *O*-alkylation and a new compound identified as γ -lactam **7a**. ^h The Ugi adduct was recovered. ⁱ Relative configuration (3*R**,4*R**)/(3*R**,4*S**). ^j Diastereoisomers were not separated, characterized as a mixture.

probably due to the low solubility of this salt in organic solvents.

To overcome this limitation, we decided to work with the more soluble cesium carbonate in the presence of an excess of lithium halides to exchange the counter cation. The use of lithium chloride (10 equiv.) improved the *C*-alkylation yield although the *O*-alkylation product was still observed (entry 6, Table 2) but, fortunately, the use of lithium iodide yielded β -lactam **6a** as a single compound (entry 7, Table 2); furthermore, the amount of this salt may be reduced to 2 equivalents without a significant decrease in chemical yield (entry 8, Table 2), except for the phenylglycine derivative **6m** (entries 2 vs. 4, Table 3). These findings could be explained not only by the smaller counter cation, lithium, which binds tightly to oxygen, but also by the Finkelstein transhalogenation reaction.¹⁶ Gratefully, this cyclization strategy proved to be general. Thus, simple refluxing of solutions of Ugi adducts **5** with a combination of cesium carbonate and lithium iodide (1.1 : 2 equiv.) in acetonitrile for 12 hours afforded in almost all cases the corresponding 2-azetidinones **6**. However, triethylamine (3 equiv.) in ethanol and ultrasonication for 2 hours proved to be most often the best choice for the cyclization of 2-chloro-2-phenylacetic derivatives (entries 16 vs. 17, Table 2) as a more efficient strategy. Therefore, this last methodology

was chosen as the cyclization strategy for the synthesis of **6i–j** and **6q–t**. In this way, we achieved chemoselective *C*-alkylation in the cyclization step from Ugi adducts **5**, crucial for our purposes in the subsequent synthesis of γ -lactams.

The stereochemical outcome in these reactions was also quite remarkable as the diastereoselectivity observed was fairly good when only one reactant incorporated a stereogenic center, but not when 2-chloro-2-phenylacetic acid (used as a racemate) was combined with α -aminoesters (entries 11–17, Table 3). In addition, the stereochemical results for the 2-chloro-2-phenylacetic acid derivatives were strongly dependent on the cyclization methodology (entry 16 vs. 17, Table 2). Nevertheless, given that the relative configuration of these lactams was not important in the next step, as it will be shown below, the isolation of diastereomers of these β -lactams was not necessary.

2.2. Synthesis of γ -lactams through expansion reactions

During the optimization studies for the synthesis of β -lactams, we gathered some valuable data about the expansion reaction. On one hand, we observed that the treatment of Ugi adduct **5a** with two equivalents of potassium carbonate (entry 3, Table 2) afforded γ -lactam **7a** as a by-product. On the other hand, the treatment of phenylglycine derivatives **5m** and **5r** with potass-



Table 3 Synthesis of β -lactams 6l–t from Ugi adducts 5l–t, all of them derived from α -aminoesters

| Entry | 5 (R ¹ , R ² , R ³ , R ⁴) | Base | Equiv. | 6 ^a (%) | d.r. ^b |
|-------|---|---|--------|---------------------|------------------------------------|
| 1 | 5l (H, C ₆ H ₅ , cC ₆ H ₁₁ , H) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6l (78) | — |
| 2 | 5m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6m (—) ^f | — |
| 3 | 5m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | NET ₃ ^d | 3 | 6m (—) ^f | — |
| 4 | 5m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | CS ₂ CO ₃ /LiI ^c | 1 : 10 | 6m (81) | — |
| 5 | 5m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | K ₂ CO ₃ ^e | 1.1 | 6m (—) ^g | — |
| 6 | 5n (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6n (90) | >98 : 2 |
| 7 | 5n (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | NET ₃ ^d | 3 | 6n (—) ^h | — |
| 8 | 5o (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6o (81) | >98 : 2 |
| 9 | 5o (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅) | NET ₃ ^d | 3 | 6o (—) ⁱ | — |
| 10 | 5p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6p (73) | >98 : 2 |
| 11 | 5q (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , H) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6q (71) | 55 : 45 ^{j,k} |
| 12 | 5q (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , H) | NET ₃ ^d | 3 | 6q (77) | 54 : 46 ^{j,k} |
| 13 | 5r (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | NET ₃ ^d | 3 | 6r (45) | 84 : 16 : n.d. : n.d. ^l |
| 14 | 5r (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | K ₂ CO ₃ ^e | 1.1 | 6r (—) ^g | — |
| 15 | 5s (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | CS ₂ CO ₃ /LiI ^c | 1 : 2 | 6s (90) | 53 : 24 : 18 : 11 ^l |
| 16 | 5s (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | NET ₃ ^d | 3 | 6s (93) | 30 : 26 : 26 : 18 ^l |
| 17 | 5t (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅) | NET ₃ ^d | 3 | 6t (75) | 58 : 35 : 7 : n.d. ^l |

^a Yield after purification. ^b Diastereomeric ratio determined by ¹H NMR. ^c In acetonitrile at reflux, 12 h. ^d In ethanol at room temperature and ultrasonication, 2 h. ^e In acetone at reflux, 12 h. ^f Complex reaction mixture. ^g Mixture of *O*-alkylation and a new compound identified as a fused pyrrolidinone-imide **8** obtained as the major product. ^h Mixture of *O*-alkylation and a new compound identified as γ -lactam **7a**. ⁱ The Ugi adduct was recovered. ^j Relative configuration (3*R**,4*R**)/(3*R**,4*S**). ^k Both diastereoisomers were separated and fully characterized. ^l Only the major diastereoisomer was isolated and fully characterized (n.d.: not detected).

ium carbonate (1.1 equiv.) afforded fused pyrrolidinone-imides **8** as the major product (entries 5 and 14, Table 3). We proposed that the syntheses of these γ -lactams probably proceeded through the expansion of the corresponding β -lactam acting as intermediate.

2.2.1. Expansion reactions on azetidines derived from activated benzyl amines. In order to demonstrate this fact, we tried the expansion to γ -lactam **7a** from the isolated β -lactam **6a**. As we expected, the treatment of this azetidione with potassium carbonate in refluxing acetone for 12 hours afforded γ -lactam **7a** almost quantitatively and, furthermore, with complete diastereoselectivity (entry 1, Table 4).

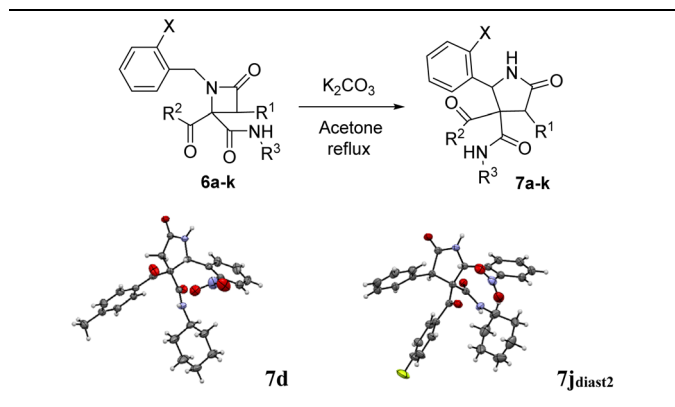
The possibility of synthesizing new, complex, and highly functionalized γ -lactams through a new and simple methodology prompted us to explore the potential of this reaction. Thankfully, all azetidione-2-ones **6** treated with carbonate afforded expansion products, although the results depended on the nature of the electron-withdrawing group (EWG) on the *N*-substituent of the β -lactam (Tables 4 and 5). Thus, for 2-nitrobenzylamine derivatives, the treatment of azetidione-2-ones **6a–k** with potassium carbonate (1.1 equiv.) in boiling acetone for 12 hours afforded the corresponding 4-acyl-4-alkylaminocarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-ones **7a–k** (Table 4). Moreover, these reactions proceeded with high diastereoselectivities. Hence, for 2-chloroacetic acid derivatives **7a–h** the observed diastereoselectivities were excellent (entries

1–8, Table 4), while for 2-chloro-2-phenylacetic acid derivatives **7i–j** only two of the four possible diastereomers were observed. We also tried the expansion on lactam **6k**, derived from benzylamine, a non-activated amine, in order to explore the influence of acidity in the benzylic position. As it was expected, azetidione **6k** was recovered after the treatment with potassium carbonate (entry 11, Table 4). However, in an attempt to achieve expansion from this lactam we tried different bases and conditions, as it will be discussed later.

2.2.2. Expansion reactions on azetidines derived from α -aminoesters. Expansion reactions for aminoester derivatives also took place, but the results were highly dependent on the nature of the aminoester and chloroacetic acid derivatives, as well as on the base used (Table 5). In this way, lactams derived from 2-chloro-2-phenylacetic acid **1b** and aminoesters afforded a major expansion product, although the chemical result depended on the relative configuration on *C4/C5*, which in turn was controlled by the size of the substituent on the aminoester (R⁴). Thus, the expansion of azetidiones derived from glycine **6q** (R⁴: H), alanine **6s** (R⁴: CH₃) and phenylalanine **6t** (R⁴: CH₂Ph) afforded the corresponding γ -lactam (**7q**, **7s** and **7t**), with a relative *trans* disposition of methoxycarbonyl substituents on *C5* and cyclohexylaminocarbamoyl groups on *C4*, which prevented the intramolecular *N*-acylation (entries 14 and 18–20, Table 5). However, phenylglycine derivative **6r** (R⁴: Ph) yielded γ -lactam **8r** fused with an imide ring resulting



Table 4 Expansion products resulting from the basic treatment of β -lactams **6a–k** derived from benzyl amines and X-Ray molecular structures of pyrrolidinones **7d** and **7jdiast2**. The ORTEP plot is at the 30% probability level



| Entry | 6 (R ¹ , R ² , R ³ , X) | 7 (%) ^a | d.r. ^b |
|-------|---|-----------------------------|------------------------------------|
| 1 | 6a (H, C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂) | 7a (90) | >98 : 2 ^c |
| 2 | 6b (H, C ₆ H ₅ , CH ₂ C ₆ H ₅ , NO ₂) | 7b (79) | 97 : 3 ^c |
| 3 | 6c (H, C ₆ H ₅ , C(CH ₃) ₃ , NO ₂) | 7c (67) | >98 : 2 ^c |
| 4 | 6d (H, 4-CH ₃ C ₆ H ₄ , cC ₆ H ₁₁ , NO ₂) | 7d (71) | 92 : 8 ^c |
| 5 | 6e (H, 4-ClC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂) | 7e (44) | >98 : 2 ^c |
| 6 | 6f (H, 4-FC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂) | 7f (42) | >98 : 2 ^c |
| 7 | 6g (H, 4-CH ₃ OC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂) | 7g (71) | >98 : 2 ^c |
| 8 | 6h (H, CH ₃ , cC ₆ H ₁₁ , NO ₂) | 7h (76) | >98 : 2 ^c |
| 9 | 6i (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , NO ₂) | 7i (92) ^d | 64 : 36 : n.d. : n.d. ^e |
| 10 | 6j (C ₆ H ₅ , 4-FC ₆ H ₄ , cC ₆ H ₁₁ , NO ₂) | 7j (91) ^d | 57 : 43 : n.d. : n.d. ^e |
| 11 | 6k (H, C ₆ H ₅ , cC ₆ H ₁₁ , H) | 7k (—) ^f | — |

^aYield after purification. ^bDiastereomeric ratio determined by ¹H NMR in the reaction mixture. ^cRelative configuration (4*R**,5*R**) in the major diastereomer, determined by NOESY and X-ray diffraction experiments. ^dYield as mixture of diastereomers. ^eRelative configuration (3*R**,4*R**,5*S**) and (3*R**,4*R**,5*R**) in the observed diastereomers, determined by NOESY and X-ray diffraction experiments. ^fAzetidione **6k** was recovered. Treatment of azetidione **6k** with different bases has been further investigated (see Scheme 3).

from the intramolecular *N*-acylation, which is explained by the relative *cis* disposition of the aforesaid substituents (entries 16 and 17, Table 5). These results were similar when cesium or potassium carbonate were employed as bases, although the use of cesium carbonate was more efficient as the reaction time was notably reduced (entry 18 vs. 19, Table 5). Moreover, the phenylglycine derivative was obtained directly from the Ugi adduct, as the higher acidity of the α -CH substituent on the nitrogen of the azetidione favored its deprotonation (entry 16, Table 5). Furthermore, a single diastereomer was observed, except for glycine derivative **7q** (R⁴: H). Nevertheless, expansion of azetidiones **6l–p**, derived from aminoesters and 2-chloroacetic acid **1a**, was highly dependent on the nature of the carbonate employed. Thus, the use of cesium carbonate gave cleaner results, yielding new bicyclic compounds **9** which resulted from expansion followed by spontaneous intramolecular *N*-acylation and debenzoylation reactions. Meanwhile, when potassium carbonate was employed, up to three different compounds were observed, γ -lactam **7**, the fused imide-lactam **8** and the debenzoylated fused imide-

lactam **9** (entries 8 and 10, Table 5). Again, the phenylglycine derivative was the only one which gave the fused γ -lactam **8m** selectively (entry 4, Table 5) starting from the corresponding Ugi adduct.

Thus, the chemical results for the aminoester series were controlled mainly by the substituents size, firstly by the C3 substitution on the γ -lactam (R¹) (entries 1–13 vs. 14–20, Table 5) and secondly by the C5 substitution (R⁴) (entries 8, 10 and 13, Table 5), which is explained by the steric hindrance exerted by the different substituents, and additionally by the nature of the carbonate employed. This shows the importance of the counter cation on the stereoselectivity of enolate reactions,¹⁷ which is reflected on the chemical result (entries 7, 9 vs. 8, 10, Table 5). These results are remarkable taking into account that ring expansion is promoted by a weak base in a wet solvent under an air atmosphere, in contrast to the strong bases and dry atmosphere needed for the ring expansion previously reported;^{10,11} moreover, high diastereoselectivities are observed in these syntheses.

2.3. Mechanism proposal for the expansion reaction

In order to understand the mechanism of expansion reactions, it is important to emphasize two significant points in their stereochemical outcome: (1) the results were independent of the diastereomeric purity of the β -lactam employed, which simplifies the experimental work to a great extent, and (2) the use of enantiomerically pure α -aminoesters leads to γ -lactams as racemates. In this way, an anionic rearrangement can be proposed starting from the deprotonation of the acidic position in the *N*-substituent of the azetidione favoring its opening, which would destroy the chiral centers on C4 and the *N*-substituent on azetidione **6**, affording an intermediate containing an imine and an enolate, which would react intramolecularly yielding the corresponding pyrrolidinone (Scheme 2).

2.4. Synthesis of debenzoylated γ -lactams

As γ -lactams fused with an imide ring **8** were debenzoylated under some of the conditions tried (entries 1–3, 5–11 and 13, Table 5), we tried the debenzoylation for the different γ -lactams synthesized, in order to obtain a new family of pyrrolidine-2-ones. Thus, the treatment of pyrrolidin-2-ones **7a–c** with a catalytic amount of potassium hydroxide in ethanol at room temperature afforded the corresponding deacylated pyrrolidin-2-one **10** as the result of a retro-Claisen reaction; moreover, only the *cis* diastereoisomer was observed by ¹H NMR in the reaction mixture (entries 1–3, Table 6). However, when we tried debenzoylation on lactams derived from 2-chloro-2-phenylacetic acid and/or α -aminoester derivatives, it was unsuccessful, probably due to steric hindrance for the former and saponification of the ester group for the latter (entries 4 and 5, Table 6).

2.5. Study of the expansion reaction on azetidine **6k**, derived from a non-activated benzyl amine

Finally, we studied the expansion on azetidione **6k**, derived from a non-activated amine. As noted above, the azetidione



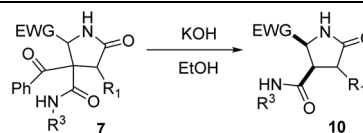
Table 5 Expansion products resulting from the basic treatment of β -lactams **6l–t** derived from α -aminoesters and X-Ray molecular structures of fused pyrrolidinone-imides **8m** and **9n**. The ORTEP plot is at the 30% probability level



| Entry | 6 (R^1, R^2, R^3, R^4) | Carbonate | Equiv. | t (h) | 7 (%) ^a | 8 (%) ^a | 9 (%) ^a |
|-------|--|--|--------|-----------------|--|---------------------------|---------------------------|
| 1 | 6l (H, C ₆ H ₅ , cC ₆ H ₁₁ , H) | CS ₂ CO ₃ | 1.2 | 1 | — | — | 9l (73) |
| 2 | 6l (H, C ₆ H ₅ , cC ₆ H ₁₁ , H) | K ₂ CO ₃ | 1.2 | 12 | 7l (18) | — | 9l (58) |
| 3 | 6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | CS ₂ CO ₃ ^{b,c} | 2.2 | 1 | — | — | 9m (65) |
| 4 | 6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | K ₂ CO ₃ ^{b,c} | 1.1 | 12 | — | 8m (83) | — |
| 5 | 6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | CS ₂ CO ₃ | 1.2 | 1 | — | 8m (30) | 9m (52) |
| 6 | 6m (H, C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | K ₂ CO ₃ | 1.2 | 12 | — | 8m (68) | 9m (12) |
| 7 | 6n (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | CS ₂ CO ₃ | 1.2 | 1 | — | — | 9n (75) |
| 8 | 6n (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | K ₂ CO ₃ | 1.2 | 12 | 7n (58) | 8n (9) | 9n (10) |
| 9 | 6o (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅) | CS ₂ CO ₃ | 1.2 | 1 | — | — | 9o (57) |
| 10 | 6o (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅) | K ₂ CO ₃ | 1.2 | 12 | 7o (38) | 8o (36) | 9o (10) |
| 11 | 6p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂) | CS ₂ CO ₃ | 1.2 | 1 | — | — | 9p (65) |
| 12 | 6p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂) | K ₂ CO ₃ | 1.2 | 12 ^d | — | 8p (5) | — |
| 13 | 6p (H, C ₆ H ₅ , cC ₆ H ₁₁ , CH(CH ₃) ₂) | K ₂ CO ₃ | 1.2 | 72 | — | 8p (78) | 9p (8) |
| 14 | 6q (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , H) | CS ₂ CO ₃ | 1.2 | 72 ^e | 7q ^f (32) ^g | — | — |
| 15 | 6q (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , H) | CS ₂ CO ₃ | 2.0 | 12 | — ^h | — | — |
| 16 | 6r (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | K ₂ CO ₃ ^{b,c} | 1.2 | 5 | — | 8r (70) | — |
| 17 | 6r (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , C ₆ H ₅) | CS ₂ CO ₃ | 1.2 | 1 | — | 8r (72) | — |
| 18 | 6s (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | K ₂ CO ₃ | 1.2 | 12 | 7s ⁱ (75) | — | — |
| 19 | 6s (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₃) | CS ₂ CO ₃ | 1.2 | 1 | 7s ⁱ (80) | — | — |
| 20 | 6t (C ₆ H ₅ , C ₆ H ₅ , cC ₆ H ₁₁ , CH ₂ C ₆ H ₅) | CS ₂ CO ₃ | 1.2 | 1 | 7t ⁱ (67) | — | — |

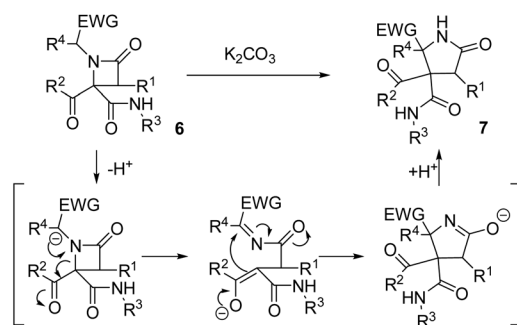
^a Yield after purification. ^b Synthesis carried out from the Ugi adduct. ^c Mixture of *O*-alkylation and expansion products. ^d After 12 h most of the azetidines was recovered. ^e After 72 h some azetidines were recovered. ^f Two diastereomers were observed (d.r. 68 : 32). ^g Yield referred to the major diastereomer after purification. ^h Complex reaction mixture. ⁱ A single diastereomer was observed.

Table 6 Debenzylation of pyrrolidine-2-ones **7**



| Entry | 4 (R^1, R^3, EWG) | 10 (%) ^a | d.r. ^{b,c} |
|-------|--|-----------------------------|---------------------|
| 1 | 7a (H, cC ₆ H ₁₁ , 2-NO ₂ C ₆ H ₄) | 10a (76) | >98 : 2 |
| 2 | 7b (H, CH ₂ C ₆ H ₅ , 2-NO ₂ C ₆ H ₄) | 10b (58) | >98 : 2 |
| 3 | 7c (H, C(CH ₃) ₃ , 2-NO ₂ C ₆ H ₄) | 10c (72) | >98 : 2 |
| 4 | 7i (C ₆ H ₅ , cC ₆ H ₁₁ , 2-NO ₂ C ₆ H ₄) | 10i (—) ^d | — |
| 5 | 7l (H, cC ₆ H ₁₁ , CO ₂ CH ₃) | 10l (—) ^e | — |

^a Yield after purification. ^b Diastereomeric ratio determined by ¹H NMR. ^c Relative configuration (4*R**,5*S**) in the major diastereomer, determined by NOESY experiments. ^d The γ -lactam was recovered. ^e Complex reaction mixture.



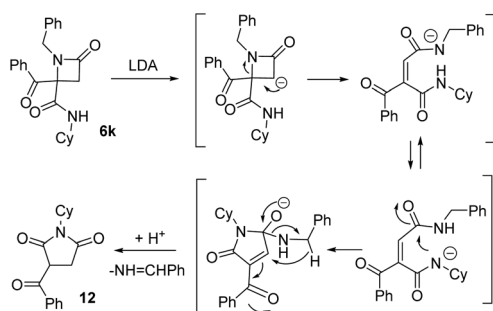
Scheme 2 Proposed mechanism for the anionic rearrangement from azetidines **6** to pyrrolidinones **7**.



Table 7 Products resulting from the basic treatment of γ -lactam **6k** derived from benzylamine


| Entry | Base | Solvent | Equiv. | 11 (%) | 7k (%) | 12 (%) |
|-------|---|---------|--------|--------|-------------------|--------|
| 1 | K ₂ CO ₃ ^a | Acetone | 1.1 | — | — | — |
| 2 | KOH ^b | EtOH | Cat. | 94 | — | — |
| 3 | LDA ^c | THF | 1.2 | 21 | 23 ^{d,e} | — |
| 4 | LDA ^c | THF | 3.0 | — | 27 ^{d,e} | 14 |

^a Reflux, 12 h. Azetidinone **6k** was recovered. ^b Ultrasonication, 30 min. ^c Room temperature, 5 h. ^d Diastereomeric ratio determined by ¹H NMR as 1 : 1. ^e Diastereoisomers were not separated.

**Scheme 3** Results for the treatment of azetidinone **6k** with base and proposed mechanism for the synthesis of succinimide **12** (Cy = cyclohexyl).

was recovered when it was treated with potassium carbonate (entry 11, Table 4). This proves the key role of acidity of the α -CH substituent on the nitrogen, so we tested stronger bases. When we tried potassium hydroxide debenzoylated azetidinone **11** was the only product observed (entry 2, Table 7). Therefore, we tried LDA in dry THF, which afforded γ -lactam **7k** but in low yield, with the result depending on the amount of base employed. Thus, when 1.2 equivalents were used, γ -lactam **7k** was obtained together with debenzoylated azetidinone **11** (entry 3, Table 7) because of the presence of traces of water in the medium. In order to reduce the formation of this compound we increased the amount of LDA employed (3.0 equiv.). In this way, the formation of azetidinone **11** was not observed, but a new compound identified as succinimide **12** was generated (entry 4, Table 7). These results highlight the importance of the nature of the *N*-substituent on the azetidine system.

This succinimide was probably generated through the competing formation of a *C*-anion on the azetidine ring. Thus, the new *C*-anion would favor the ring opening to a diamide anion, which after an intramolecular cyclization to a five-member

ring followed by an intramolecular Cannizzaro-type reaction, would afford imide **12** (Scheme 3).

3. Conclusions

These results show the versatility of Ugi adducts in the synthesis of highly functionalized *N*-heterocycles through post-condensation reactions. Different ring-size lactams with different substituents have been synthesized using simple protocols, in many cases with a high diastereoselectivity. Moreover, the rational design of Ugi adducts allows the synthesis of β -lactams which rearrange to γ -lactams using simple, economical and low moisture-sensitive bases, in an air atmosphere and in a robust manner. Interestingly, the substitution patterns achieved in some structures have not been reported before.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Funding from Consejería de Educación de la Junta de Castilla y León and European Regional Development Fund (ERDF) (project BU075G19 and project BU067P20) and MCIN/AEI/10.13039/501100011033 [grant PID2020-117610RB-I00] is gratefully acknowledged. B. G.-S. and I. C.-B. thank Consejería de Educación de la Junta de Castilla y León, European Social Fund (ESF) and ERDF for their predoctoral (B. G.-S) and postdoctoral (I. C.-B.) contracts.

References

- (a) *Heterocycles in Life and Society*, ed. A. F. Pozharskii, A. T. Soldatenkov and A. R. Katrizky, John Wiley & Sons, Ltd, 2nd edn, 2011, pp. 209–244; (b) C. Lamberth, *Pest Manage. Sci.*, 2013, **69**, 1106–1114; (c) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- (a) A. Lei, J. P. Waldkirch, M. He and X. Zhang, *Angew. Chem., Int. Ed.*, 2002, **41**, 4526–4529; (b) P. Y. Ng, Y. Tang, W. M. Knosp, H. S. Stadler and J. T. Shaw, *Angew. Chem., Int. Ed.*, 2007, **46**, 5352–5355; (c) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156–1171; (d) R. Narayan, M. Potowski, Z. J. Jia, A. P. Antonchick and H. Waldmann, *Acc. Chem. Res.*, 2014, **47**, 1296–1310; (e) A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129–133; (f) N. Fuentes, W. Kong, L. Fernández-Sánchez, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2015, **137**, 964–973; (g) A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones and O. Fadeyi, *Org. Biomol. Chem.*, 2016, **14**, 6611–6637; (h) A. Geranurimi and W. D. Lubell, *Org. Lett.*, 2018, **20**,



- 6126–6129; (i) A. Tyszka-Gumkowska and J. Jurczak, *Org. Chem. Front.*, 2021, **8**, 5888–5894; (j) L.-S. Wu, Y. Ding, Y.-Q. Han and B.-F. Shi, *Org. Lett.*, 2021, **23**, 2048–2051.
- 3 For the synthesis of β -lactams see: (a) C. R. Pitts and T. Lectka, *Chem. Rev.*, 2014, **114**, 7930–7953; (b) S. Hosseini and A. Jarrahpour, *Org. Biomol. Chem.*, 2018, **16**, 6840–6852. For the synthesis of γ -lactams see: (c) F. Rivas and T. Ling, *Org. Prep. Proced. Int.*, 2016, **48**, 254–295; (d) J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156.
- 4 (a) S. Dandapani and L. A. Marcaurelle, *Nat. Chem. Biol.*, 2010, **6**, 861–863; (b) A. Barker, J. G. Kettle, T. Nowak and J. E. Pease, *Drug Discovery Today*, 2013, **18**, 298–304.
- 5 S. Comesse, M. Sanselme and A. Daïch, *J. Org. Chem.*, 2008, **73**, 5566–5569.
- 6 B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107**, 4437–4492.
- 7 (a) B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo and M. P. Ruiz, *J. Org. Chem.*, 2013, **78**, 10154–10165; (b) B. Alcaide, P. Almendros, R. Martín-Montero and M. P. Ruiz, *Adv. Synth. Catal.*, 2016, **358**, 1469–1477.
- 8 (a) S. Kano, T. Ebata and S. Shibuya, *Chem. Pharm. Bull.*, 1979, **27**, 2450–2455; (b) T. J. Fleck, W. W. McWhorter Jr., R. N. DeKam and B. A. Pearlman, *J. Org. Chem.*, 2003, **68**, 9612–9617.
- 9 (a) W. Van Brabandt and N. De Kimpe, *J. Org. Chem.*, 2005, **70**, 3369–3374; (b) W. Van Brabandt, R. Van Landeghem and N. De Kimpe, *Org. Lett.*, 2006, **8**, 1105–1108; (c) S. Dekeukeleire, M. D'Hooghe and N. De Kimpe, *J. Org. Chem.*, 2009, **74**, 1644–1649; (d) M. D'hooghe, S. Dekeukeleire, E. Leemans and N. De Kimpe, *Pure Appl. Chem.*, 2010, **82**, 1749–1759.
- 10 T. Durst, R. Van Den Elzen and M. J. LeBelle, *J. Am. Chem. Soc.*, 1972, **94**, 9261–9263.
- 11 (a) J. Escalante and M. A. Gonzalez-Tototzin, *Tetrahedron: Asymmetry*, 2003, **14**, 981–985; (b) T. Sakai, K. Yamada and K. Tomioka, *Chem. – Asian J.*, 2008, **3**, 1486–1493; (c) M.-J. Lee and C. Ahn, *Bull. Korean Chem. Soc.*, 2016, **37**, 580–583.
- 12 (a) Z. Xu, F. De Moliner, A. P. Cappelli and C. Hulme, *Angew. Chem., Int. Ed.*, 2012, **51**, 8037–8040; (b) U. K. Sharma, N. Sharma, D. D. Vachhani and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2015, **44**, 1836–1860; (c) Y. He, Z. Li, K. Robeyns, L. Van Meervelt and E. V. Van der Eycken, *Angew. Chem., Int. Ed.*, 2018, **57**, 272–276; (d) S. Wang, Y. Tao, J. Wang, Y. Tao and X. Wang, *Chem. Sci.*, 2019, **10**, 1531–1538; (e) K. Singh, B. K. Malviya, P. K. Jaiswal, V. P. Verma, S. S. Chimni and S. Sharma, *Org. Lett.*, 2019, **21**, 6726–6730.
- 13 X.-H. Zeng, H.-M. Wang, Y.-M. Yan, L. Wu and M.-W. Ding, *Tetrahedron*, 2014, **70**, 3647–3652.
- 14 P. Pertejo, A. Sancho-Medina, T. Hermosilla, B. González-Saiz, J. Gómez-Ayuso, R. Quesada, D. Moreno, I. Carreira-Barral and M. García-Valverde, *Molecules*, 2021, **26**, 919.
- 15 L. M. Jackman and B. C. Lange, *Tetrahedron*, 1977, **33**, 2737–2769.
- 16 H. Finkelstein, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 1528–1532.
- 17 Y. Hu, R. L. Bishop, A. Luxenburger, S. Dong and L. A. Paquette, *Org. Lett.*, 2006, **8**, 2735–2737.

