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# Straightforward Access to a Great Diversity of Complex Biorelevant $\gamma$ -Lactams Thanks to a Tunable Cascade Multicomponent Process

Muhammad Idham Darussalam Mardjan, Atef Mayooufi, Jean-Luc Parrain, Jérôme Thibonnet,\* and Laurent Commeiras\*

**ABSTRACT:** This reviews surveys the preparation of a great diversity of complex biorelevant  $\gamma$ -lactam backbones thanks to scalable copper(I)-catalyzed cascade multicomponent processes.

**KEYWORDS:** lactams, copper catalysis, heterocyclic compounds, multicomponent reaction,  $\gamma$ -hydroxybutyrolactams, spiro lactams

## 1. INTRODUCTION

1*H*-Pyrrol-2(*5H*)-ones **1** represent important heterocycles found in many natural products and molecules with a variety of pharmaceutical uses.<sup>1</sup> Several examples possessing interesting structural and biological activities include codinaeopsin (**2**),<sup>2</sup> axinellamide (**3**),<sup>3</sup> pulchellalactam (**4**),<sup>4</sup> pandamarine (**5**),<sup>5</sup> and erysotramidine (**6**)<sup>6</sup> (Figure 1). Among them, 5-hydroxy-1*H*-pyrrol-2(*5H*)-ones **7**, also known as  $\gamma$ -hydroxy- $\gamma$ -lactams, have attracted a lot of interest because of their versatility in organic synthesis and medicinal chemistry.<sup>7</sup> As a consequence, a number of synthetic strategies have been devised to access these heterocycles, including intra- and intermolecular routes as well as oxidation reactions of heterocyclic compounds.<sup>8</sup> More specifically, several groups have designed efficient and attractive routes based on multicomponent reactions (MCRs)<sup>9</sup> to address the modular preparation of these  $\gamma$ -hydroxy- $\gamma$ -lactams **7**.

These MCRs mainly involve a three-component reaction of aldehydes, 1,3-dicarbonyl compounds, and isocyanides;<sup>10</sup> dialkyl acetylenedicarboxylates, benzoyl chlorides, and isocyanides;<sup>11</sup> primary amines, dimethyl acetylenedicarboxylate, and oxalyl chloride;<sup>12</sup> or dibenzoylacetylene, aryl sulfonyl isocyanates, and amines.<sup>13</sup> More recently, an elegant enantioselective MCR of ketones, carboxylic acids, and nitroalkenes catalyzed by a chiral proline ester derivative has been also reported by Cossío and co-workers.<sup>14</sup>

In addition, it was reported in 2009 that the palladium-free Sonogashira coupling between (*Z*)-3-iodoacrylic acids **8** and terminal alkynes **9**, followed by a 5-*exo*-dig oxa-cyclization, offered a convenient access to  $\gamma$ -alkylidenebutenolides **10** (Scheme 1a).<sup>15,16</sup> It is also generally known that treatment of  $\gamma$ -alkylidenebutenolides **10** with primary amines **11** leads to the formation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams **7** (Scheme 1a), and this approach is commonly used.<sup>17,18</sup> Moreover, treatment of  $\gamma$ -hydroxybutyrolactams **7** with acid sources results in the formation of the corresponding *N*-acyliminium ions **12**, which can evolve either to  $\gamma$ -alkylidene- $\gamma$ -butyrolactams **13**<sup>19</sup> or  $\gamma$ -functionalized lactams **14**<sup>20</sup> (Scheme 1a). By taking advantage of these transformations, Commeiras and co-workers proposed new multicomponent synthetic strategies using readily or

commercially available (*Z*)-3-iodoacrylic acids as well as (*E*)-2,3-dihaloacrylic acids **8**, terminal alkynes **9**, and primary amines **11** in the presence of a copper(I) catalyst to provide either  $\gamma$ -hydroxy- $\gamma$ -butyrolactams **7** or various  $\gamma$ -lactam motifs **13–16**.<sup>21,22</sup> In this review, we provide a comprehensive survey of this copper(I)-mediated multicomponent process, which could be compared to a (3 + 1 + 1) ring construction cyclization approach, that enables the preparation, in a simple and atom-economical transformation, of a great diversity of complex biorelevant  $\gamma$ -hydroxy- $\gamma$ -butyrolactams **7** and their one-pot postfunctionalization (Scheme 1b).

## 2. SYNTHESIS OF $\gamma$ -HYDROXYBUTYROLACTAMS **7**

Initially, the authors have shown that the optimum reaction conditions were obtained when the process was conducted in degassed *i*-PrOH at 50 °C for 12 h using 1 equiv of the acrylic acid ((*Z*)-3-iodobut-2-enoic acid (**8a**)), 2 equiv of the terminal alkyne (phenylacetylene (**9a**)), and 2 equiv of the primary amine (butylamine (**11a**)) along with 2 equiv of K<sub>2</sub>CO<sub>3</sub> and 20 mol % CuI.<sup>15</sup> Under these conditions,  $\gamma$ -hydroxy- $\gamma$ -butyrolactam **7a** was obtained in an excellent 84% isolated yield on a 2 mmol scale (Scheme 1). It is worth noting that **7a** was prepared by means of a one-pot palladium-free Sonogashira coupling/heterocyclization/nucleophilic addition cascade in which one C–C, one C–O, and two C–N bonds were created without the formation of side products arising from the potential reactions such as Ullmann coupling and 1,4- and 1,6-conjugate addition between the lactone intermediate **10a** and the primary amine. In addition, the scale-up to 20 mmol of **8a** was readily accomplished without requiring the optimization of the previous reaction conditions. The product **7a** was isolated in the same excellent yield (82%, 4.27 g).

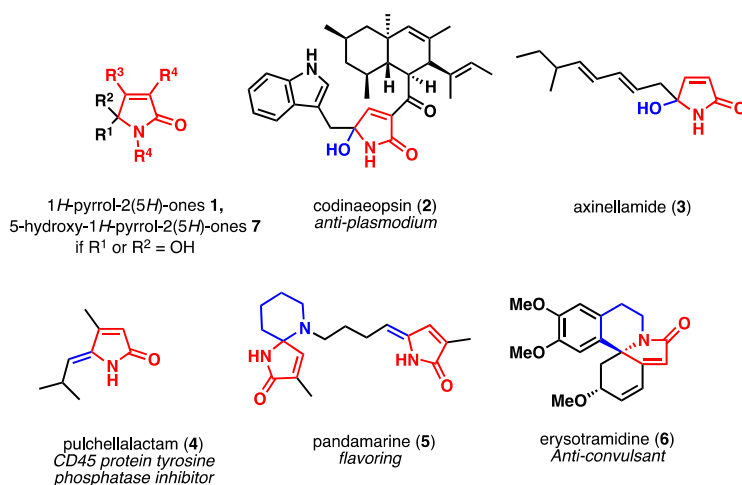
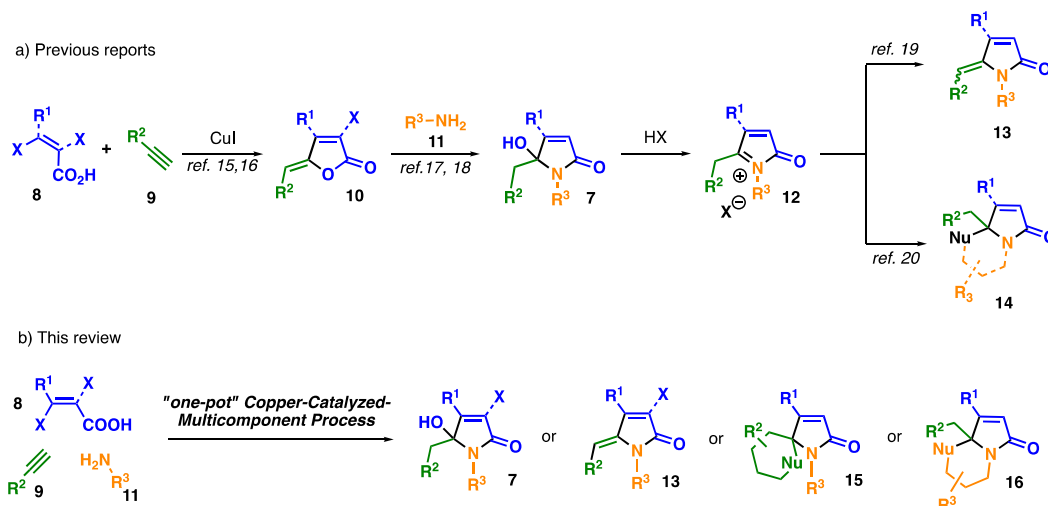


Figure 1. Natural products containing the  $\gamma$ -lactam moiety.

Scheme 1. Proposed Cascade Strategies for Direct Synthesis of Various  $\gamma$ -Lactam Motifs

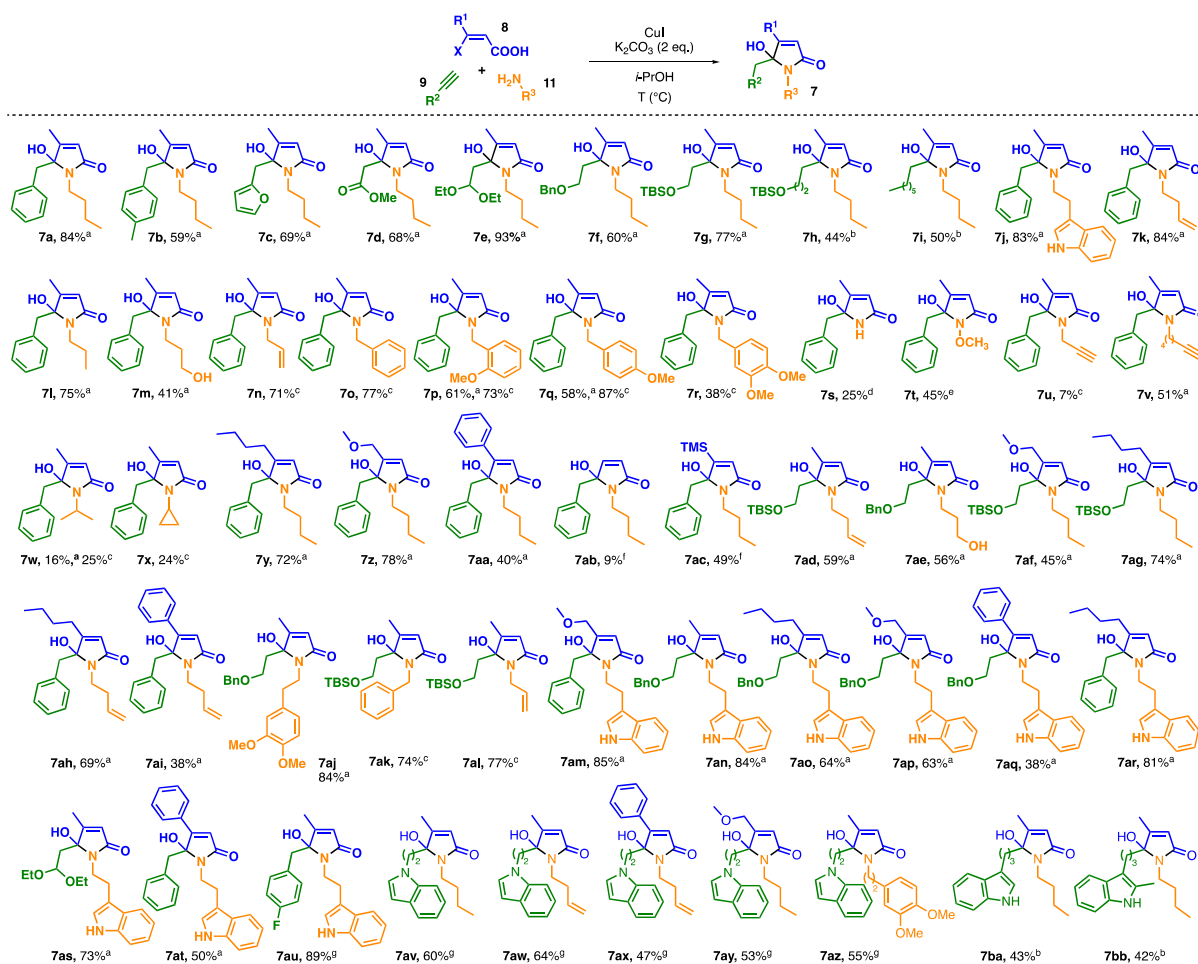


The applicability and generality of this process has been demonstrated by the preparation of a large library (more than 60 examples) of  $\gamma$ -hydroxybutyrolactams **7** (Schemes 2 and 3). Indeed, diversely substituted and functionalized starting materials are tolerated and have been converted to the desired targets **7**.

Terminal alkynes bearing both aromatic and heteroaromatic rings and terminal alkynes substituted with different functional groups such as methyl ester, diethyl acetal, and benzyl as well as silicon-protected propargyl alcohol are tolerated in the multicomponent reaction. Application of alkynes containing longer aliphatic chains such as *tert*-butyldimethylsilyl (TBS)-protected but-4-ynol and oct-1-yne, produced the corresponding lactams **7h** and **7i** but in lower yields (up to 50%) because of the formation of six-membered lactones (13% and 10%, respectively, as the thermodynamic products generated from the 6-*endo* heterocyclization step).<sup>23</sup> Unfortunately, these six-membered lactones are unreactive toward primary amines. For these nonactivated alkynes, the optimization of the reaction conditions revealed that it is necessary to perform the reaction at

45 °C in the presence of 4 equiv of the primary amine to obtain better results. The authors found that this reaction was dependent on the nucleophilicity of the primary amine **11**. Compared with nucleophilic amines, such as butylamine, tryptamine, homoallylamine, and propylamine, for which only 2 equiv is required, 3 equiv of amines possessing less nucleophilic character (e.g., allylamine and benzylamine) was necessary to completely convert lactone intermediates **10** into the corresponding  $\gamma$ -hydroxy- $\gamma$ -lactams **7**. In the case of 2-methoxybenzylamine and 4-methoxybenzylamine, the reaction could be conducted using 2 equiv of the corresponding primary amine to give the desired products **7p** and **7q** but in lower yields (61% and 58%, respectively) compared with the use of 3 equiv of **11**. The major limitation of the reaction was obtained with weakly nucleophilic aniline derivatives (aniline and 4-methoxyaniline), since the corresponding hydroxylactams **7** were not detected. The weakly nucleophilic behavior of a non-alkyl primary amine was also observed with ammonia. The resulting scaffold **7s** was isolated in moderate yield (25%) even when 10 equiv of NH<sub>3</sub> solution (2 M in *i*-PrOH) was used for 48 h. It is

Scheme 2. Scope of the MCR Process



<sup>a</sup>1 equiv of **8**, 2 equiv of **9**, 2 equiv of **11**, 20 mol % CuI, 50 °C, 12 h. <sup>b</sup>1 equiv of **8**, 2 equiv of **9**, 4 equiv of **11**, 20 mol % CuI, 45 °C, 12 h. <sup>c</sup>1 equiv of **8**, 2 equiv of **9**, 3 equiv of **11**, 20 mol % CuI, 50 °C, 12 h. <sup>d</sup>1 equiv of **8**, 2 equiv of **9**, 10 equiv of **11**, 20 mol % CuI, 50 °C, 48 h. <sup>e</sup>1 equiv of **8**, 2 equiv of **9**, 3 equiv of **11**, 20 mol % CuI, 6 equiv of NEt<sub>3</sub>, 50 °C, 72 h. <sup>f</sup>1 equiv of **8**, 2 equiv of **9**, 2 equiv of **11**, 1 equiv of CuI, 50 °C, 12 h. <sup>g</sup>1 equiv of **8**, 2 equiv of **9**, 3 equiv of **11**, 1 equiv of CuI, 50 °C, 12 h.

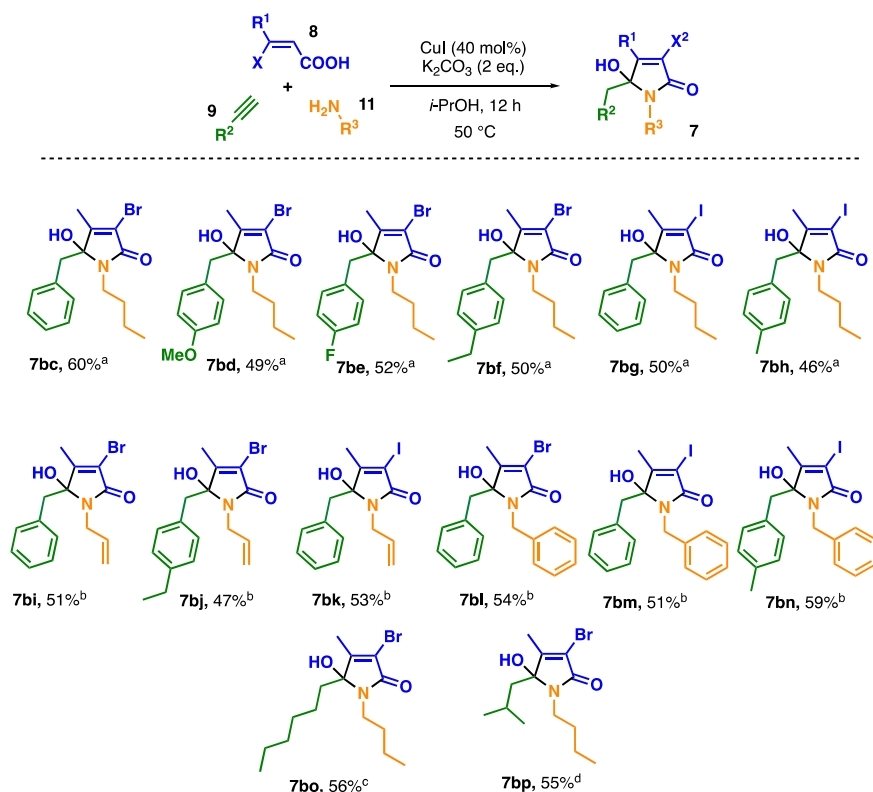
worth mentioning that a beneficial  $\alpha$  effect occurred starting from methoxyamine hydrochloride; **7t** was isolated in better yield (45%).

The chemoselectivity of the multicomponent process was also assessed by using alkynylamine substrates such as propargylamine and hex-5-ynylamine. While a low isolated yield of hydroxylactam **7u** (7%) was observed with propargylamine (even with 3 equiv), hydroxylactam **7v** was obtained in moderate yield (51%) starting from hex-5-ynylamine. This result demonstrated that the Sonogashira coupling exclusively favored the triple bond of terminal aromatic alkynes compared with that of alkynylamines. The steric effect on the efficiency of the cascade process was also evaluated. When isopropylamine was used as the primary amine under otherwise standard conditions, a 1:0.5 mixture of the desired lactam **7w** and the residual alkylidenebutenolide **10w** was formed. Compared with hydroxylactam isomer **7l**, which was isolated in 75% yield, **7w** was isolated in 16% yield. The presence of lactone **10w** would indicate that steric hindrance may inhibit the nucleophilic addition reaction of the primary amine. Increasing the amount of

primary amine to 3 equiv gave full conversion to hydroxylactam **7w**, unfortunately with a slight increase in the yield (25%). It has been also shown that various substituents can be installed at the  $\beta$ -position of the iodoacrylic acid to effectively produce the desired  $\gamma$ -hydroxylactams. It should be noted that  $\alpha,\beta$ -unsubstituted  $\gamma$ -hydroxy- $\gamma$ -lactam moiety **7ab** could not be generated in good yield (9%) starting from (*Z*)-3-iodopropenoic acid. This low isolated yield could be explained by the formation of side products arising from the 1,4-conjugate addition reaction and the low stability of the lactam.<sup>24</sup> As an alternative pathway,  $\gamma$ -lactam **7ab** could be obtained in a two-step procedure by installing a temporary disposable trimethylsilyl group at the  $\beta$ -position. Indeed, the reaction was conducted using (*Z*)-3-iodo-3-(trimethylsilyl)propenoic acid with 1 equiv of copper(I) iodide to give  $\beta$ -silylated hydroxylactam **7ac** in 49% yield, which in turn underwent the desilylation reaction using NaF to furnish **7ab** in 57%.

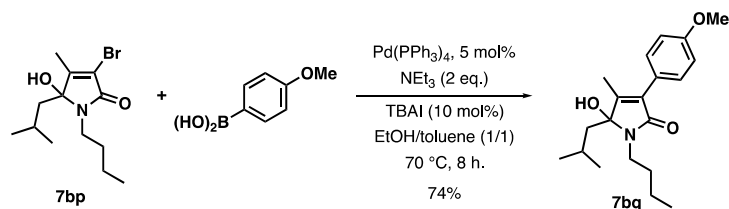
Special attention was paid to the introduction of an indole moiety in order to gain rapid access to biorelevant  $\gamma$ -hydroxybutyrolactam/indole hybrid scaffolds. For this purpose,

Scheme 3. Preparation of  $\alpha$ -Halogeno- $\gamma$ -hydroxybutyrolactams



<sup>a</sup>1 equiv of 8, 2 equiv of 9, and 2 equiv of 11. <sup>b</sup>1 equiv of 8, 2 equiv of 9, and 3 equiv of 11. <sup>c</sup>1 equiv of 8, 2 equiv of 9, and 4 equiv of 11. <sup>d</sup>1 equiv of 8, 5 equiv of 9, and 3 equiv of 11.

Scheme 4. Preparation of  $\alpha$ -Substituted  $\gamma$ -Hydroxybutyrolactam 7bq



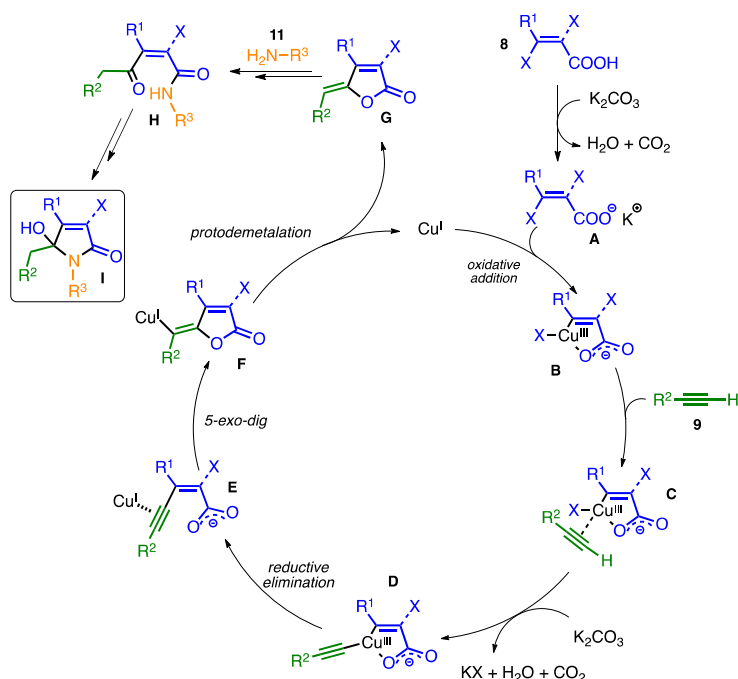
the indole nucleus could be incorporated either on the primary amine (starting from tryptamine) or on the terminal alkyne (starting from *N*-propargylindole or 3-(but-3-yn-1-yl)-1*H*-indole). Whatever the nature of the starting materials, the desired hybrid scaffolds **7am–bb** were successfully prepared up to 89% yield. It is worth noting that when *N*-propargylindole was applied as a starting material, 1 equiv of CuI and 3 equiv of primary amine were required to achieve complete conversion of the lactone intermediate. As previously discussed, in the case of nonactivated 3-(but-3-yn-1-yl)-1*H*-indoles, the desired  $\gamma$ -hydroxybutyrolactams **7ba** and **7bb** were prepared in moderate yields (43% and 42%, respectively) together with the undesired pyran-2-ones (in ratios of 1:0.22 and 1:0.22, respectively).

Finally, in order to increase the molecular complexity of the  $\gamma$ -hydroxybutyrolactams, this process was also assessed starting from  $\alpha,\beta$ -dihalogenoacrylic acids (Scheme 3).<sup>25</sup> In this case, the copper-mediated MCR furnished  $\alpha$ -halogeno- $\gamma$ -hydroxybutyr-

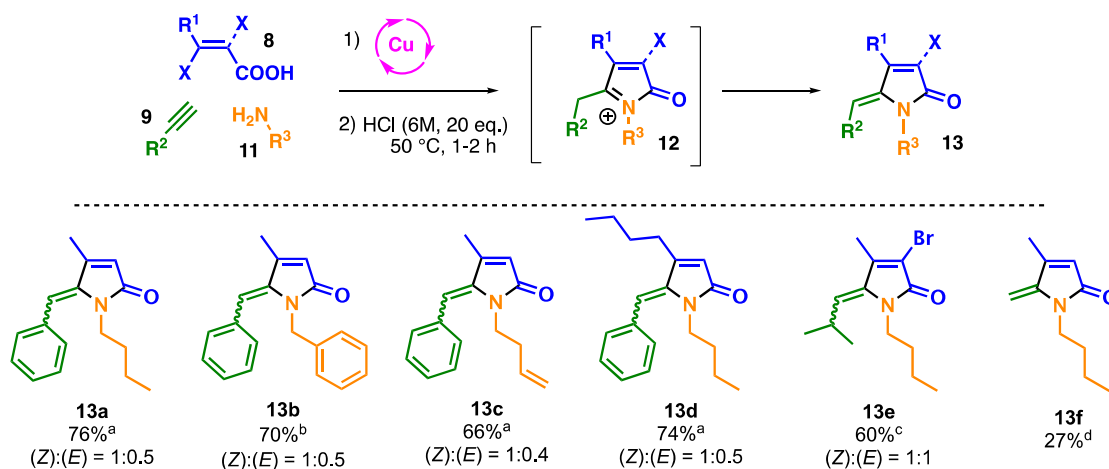
olactams, allowing postfunctionalization at the  $\alpha$ -position by exploiting the reactivity of the resultant halogen atom. The utilization of  $\alpha,\beta$ -dibromobutenoic acid or  $\alpha,\beta$ -diiodobutenoic acid required a slight modification of the reaction conditions. The best results were observed when the reaction was conducted with 40 mol % CuI at 55 °C. Under these conditions, several  $\alpha$ -halogeno- $\gamma$ -hydroxybutyrolactams were prepared in moderate yields (up to 60%) by varying both the nature of the terminal alkyne and the primary amine. As previously, the reaction was scaled-up to 20 mmol without loss of efficiency. **7bc** was isolated in 52% yield. Interestingly, when **7bp** was exposed to *p*-methoxyphenylboronic acid, the Pd-catalyzed Suzuki–Miyaura coupling reaction led to the formation of  $\alpha$ -substituted  $\gamma$ -hydroxybutyrolactam **7bq** in 74% yield (Scheme 4).

Two mechanistic scenarios could be considered for this copper-mediated multicomponent process. The first one would involve a Castro–Stephens-type coupling, whereas the second

Scheme 5. Plausible Mechanism for the Preparation of 7



Scheme 6. Cascade Multicomponent Process toward the Synthesis of  $\gamma$ -Alkylidene- $\gamma$ -lactams 13



<sup>a</sup>1 equiv of 8, 2 equiv of 9, 2 equiv of 11, 20 mol % CuI, 50 °C. <sup>b</sup>1 equiv of 8, 2 equiv of 9, 3 equiv of 11, 20 mol % CuI. <sup>c</sup>1 equiv of 8, 5 equiv of 9, 3 equiv of 11, 20 mol % CuI. <sup>d</sup>(1) 1 equiv of 8, 5 equiv of 9, 2 equiv of 11, 100 mol % CuI, 75 °C, 12 h; (2) HCl (6 M, 20 equiv), 75 °C.

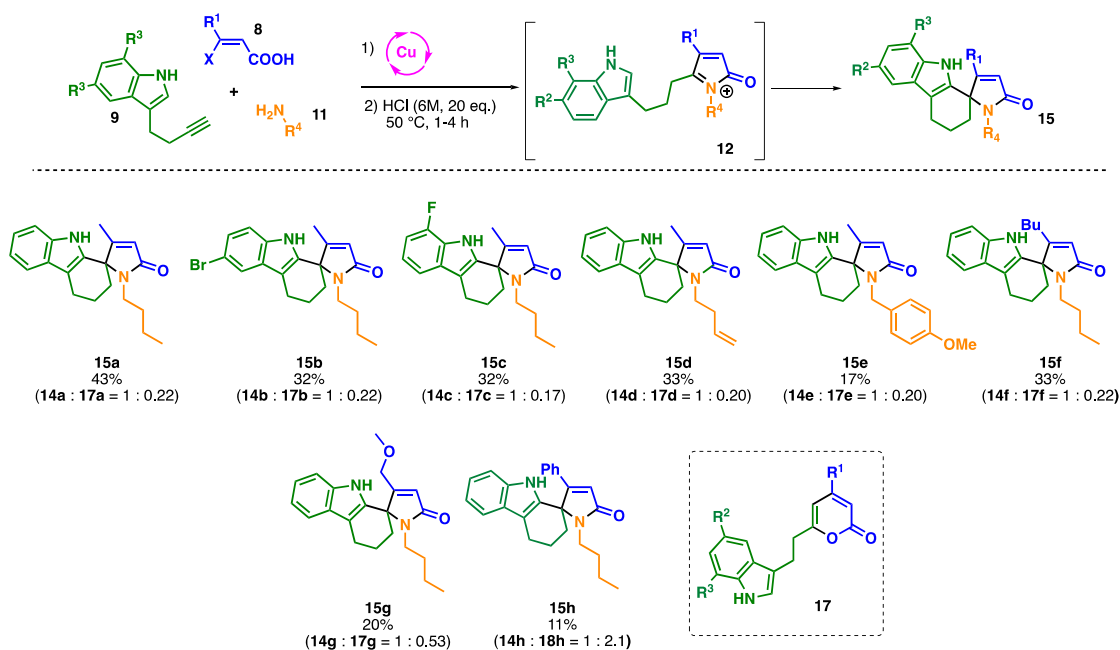
one would proceed by a Sonogashira-type coupling (without palladium). The Castro–Stephens-type coupling is disregarded because when the reaction to form lactone 10 was performed with 1 equiv of phenylethynylcopper reagent and (Z)-3-iodobut-2-enoic acid 8a, no lactone 10a was observed in the crude mixture. Therefore, a plausible mechanism based on a Sonogashira-type coupling without palladium is depicted in Scheme 5. The first step is likely to be oxidative addition of copper(I) into the C–I bond of A to give copper(III) intermediate B. The next steps would involve  $\pi$  coordination of the alkyne reagent followed by the formation of complex D via base-mediated deprotonation of the terminal acetylenic proton.

Next, reductive elimination of intermediate D followed by 5-exo-dig cyclization assisted by copper(I) would lead to vinylcopper intermediate F, which would give lactone G via protodemetalation. Finally, nucleophilic addition of the primary amine onto lactone G would furnish the desired hydroxylactam I via intermediate H.

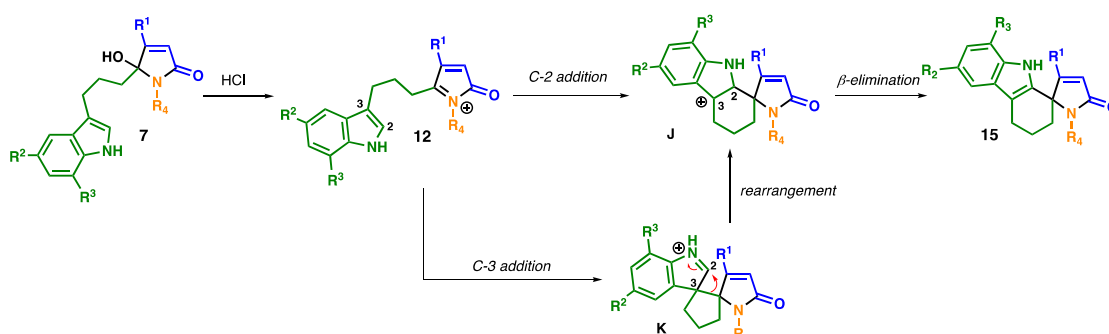
### 3. ONE-POT POSTFUNCTIONALIZATION OF 7

Encouraged by the excellent results obtained with this copper(I)-catalyzed cascade multicomponent process, Commeiras and co-workers then investigated the synthetic application of  $\gamma$ -hydroxy- $\gamma$ -lactams 7 by exploiting their

Scheme 7. Cascade Multicomponent Process toward the Synthesis of (5,6)-Spirolactams 15



Scheme 8. Plausible Mechanism for the Formation of Spirolactams 15



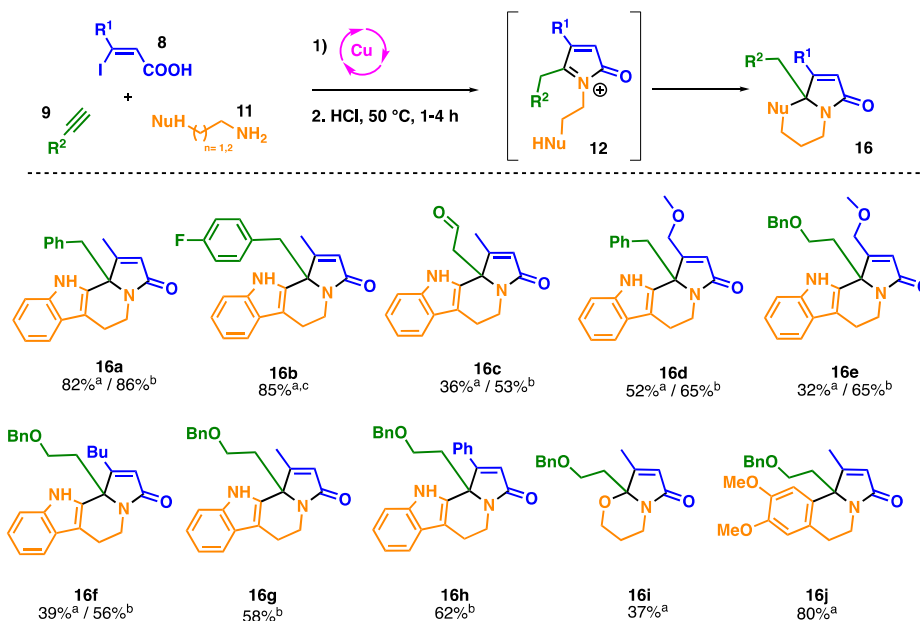
reactivity as *N*-acyliminium ion (NAI) precursors **12**.<sup>24,26,27</sup> Indeed, NAIs are highly reactive electrophilic intermediates, and they are therefore excellent candidates for the creation of both carbon–carbon and carbon-heteroatom bonds. The purpose was to extend the previous multicomponent process by carrying out the formation and postfunctionalization of NAIs in a one-pot fashion. The incorporation of the NAI chemistry into the cascade process was carried out simply by quenching the copper(I)-catalyzed multicomponent reaction with an aqueous HCl solution instead of a saturated aqueous NH<sub>4</sub>Cl solution.

In the absence of any potential nucleophiles, the NAI intermediates **12** underwent a  $\beta$ -elimination reaction to give the corresponding  $\gamma$ -alkylidene- $\gamma$ -lactams **13** as inseparable mixtures of diastereomers in good yields (Scheme 6). Importantly, this strategy allowed  $\gamma$ -methylidenebutyrolactam **13f** (54% brsm) to be obtained in a very convergent way compared with those described in the literature for such scaffolds.<sup>28</sup> In this case, ethynyltrimethylsilane played the role of an acetylene equivalent. It is worth noting that the moderate yield observed

is presumably due to a low conversion rate of the reaction (50%).

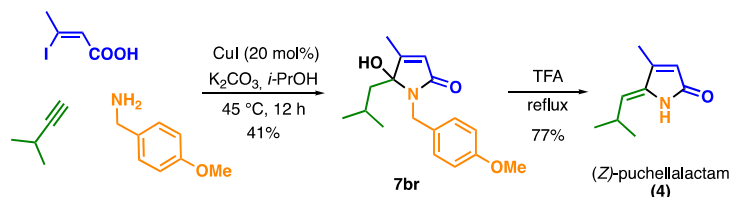
On the contrary, in the presence of nucleophiles, the NAI intermediates **12** could be trapped. Thanks to an intramolecular reaction and depending on the position of the nucleophiles, the synthesis of different polyheterocyclic lactams **15** and **16** was envisaged. Indeed, while the installation of the nucleophilic site in the terminal alkynes provided the corresponding spirolactams **15**, nucleophile-substituted primary amines provided fused-heterocycle lactam derivatives **16**. The authors showed that (5,6)-spirolactams **15** were generated when nonactivated indole-substituted terminal alkynes **9**, namely, 3-(but-3-yn-1-yl)-1*H*-indole derivatives were subjected to the process (Scheme 7). The tolerable yields of **15** are generally due to the formation of a 20% yield of the undesired and unreactive six-membered lactones **17**. Even if the yields of the isolated desired products are relatively moderate, this useful cascade multicomponent process allows the synthesis of (5,6)-spirocyclic scaffolds via the construction of two C–C and two C–N bonds together with a quaternary center from readily available starting materials.

Scheme 9. Cascade Multicomponent Process toward Polyheterocyclic Lactam Derivatives 16



<sup>a</sup>HCl (6 M, 20 equiv). <sup>b</sup>HCl (1 M, 7 equiv). <sup>c</sup>Tryptamine (3 equiv) and CuI (1 equiv).

Scheme 10. Total Synthesis of (*Z*)-Puchellactam (4)



Concerning the mechanism for the formation of the corresponding spiro lactams, the nucleophilic addition of the indole moiety may occur from either C-2 or C-3 (Scheme 8). The C-2 addition would produce carbocation J, which in turn would undergo  $\beta$ -elimination to give the desired spiro lactam 15. On the other hand, the C-3 addition would provide the spiro compound intermediate K. The latter would undergo rearrangement to give J, followed by  $\beta$ -elimination to furnish the final product 15.

Performing the same previous multicomponent process (copper(I)-catalyzed multicomponent process followed by sequential addition of 6 M aqueous HCl solution) by mixing tryptamine, different terminal alkynes, and (*Z*)-3-iodoprop-2-enoic acid derivatives allowed the formation of polyheterocycles **16a–h** containing a tetrahydro- $\beta$ -carboline moiety in moderate to very good yields through an intramolecular C-2 Friedel–Crafts alkylation (Scheme 9). Attempts to improve the effectiveness of the cascade process were successfully conducted by using a less concentrated aqueous solution of HCl (1 M). Under that condition, the polyheterocyclic compounds were obtained in better yields (53–86%). It is worth noting that this cascade process was scaled-up to 20 mmol. Under those conditions, **16a** was obtained in 61% yield (4 g). It was also demonstrated that the application of 3-aminopropanol afforded another polyheterocyclic scaffold, namely, oxazinopyrrolone

**16i**, in 37% yield. Moreover, the extended cascade process could be exploited to directly produce (in 80% yield) polyheterocycle **16j**, a scaffold found in the natural product erysothramidine (6).

Lastly, in addition to these systematic studies, the utility of the copper(I)-mediated MCR process was nicely illustrated by the total synthesis of the natural product (*Z*)-puchellactam (4), which is an inhibitor of the CD45 protein tyrosine phosphatase,<sup>4</sup> in a two-step procedure ( $\gamma$ -hydroxybutyrolactam formation followed by dehydration) from (*Z*)-3-iodobut-2-enoic acid, isopropylacetylene, and *N*-*p*-methoxybenzylamine (Scheme 10). Indeed, by the use of slightly modified conditions (4 equiv of isopropylacetylene and 3 equiv of *p*-methoxybenzylamine),  $\gamma$ -hydroxybutyrolactam **7br** was obtained in 41% yield. Compound **7br** was then subjected to TFA to give a separable 9:1 mixture of (*Z*)- and (*E*)-puchellactam, from which the natural product was isolated in 77% yield.

#### 4. SUMMARY

Several methods to synthesize  $\gamma$ -hydroxy- $\gamma$ -butyrolactams have been reported in the literature. However, strategies based on multicomponent reactions (MCRs) to address the modular preparation of these scaffolds are the most suitable. In this context, a scalable and tunable cascade multicomponent process starting from readily available (*Z*)-3-iodoacrylic or (*E*)-2,3-dihaloenoacrylic acids, terminal alkynes, and primary amines in

the presence of a copper(I) catalyst was developed, allowing the preparation of large library of hydroxylactams. It was also demonstrated that the cascade reaction could be extended by exploiting the chemistry of  $\gamma$ -hydroxy- $\gamma$ -lactams as equivalents of *N*-acyliminium ions. A high diversity of  $\gamma$ -alkylidene- $\gamma$ -lactams, spiro-lactams, and polyheterocyclic lactams can be simply accessed in a single operation.

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### Notes

The authors declare no competing financial interest.

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