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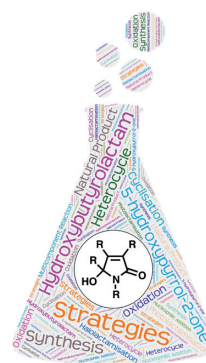
# Strategies To Access $\gamma$ -Hydroxy- $\gamma$ -butyrolactams

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**Abstract**  $\alpha,\beta$ -Unsaturated  $\gamma$ -hydroxy- $\gamma$ -butyrolactams are of a great interest due to their presence in designed pharmaceutical molecules and numerous natural products displaying a broad spectrum of biological activities. In addition, these five-membered heterocyclic compounds are also relevant and versatile building blocks in organic synthesis. In this context, strategies for the construction of these scaffolds has triggered considerable attention and this review highlights the progress in the formation of  $\alpha,\beta$ -unsaturated  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones).

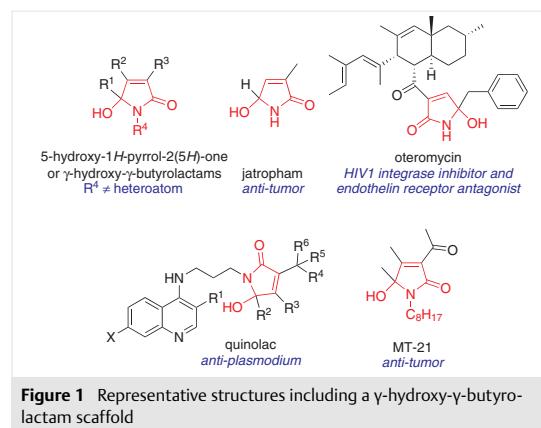
- 1 Introduction
- 2 Intramolecular Routes
- 3 Intermolecular Routes
- 4 Oxidation of Heterocyclic Compounds
- 5 Miscellaneous
- 6 Conclusion

**Key words**  $\gamma$ -hydroxy- $\gamma$ -butyrolactam, 5-hydroxy-1,5-dihydro-2H-pyrrol-2-one, heterocycle, synthesis, strategies, natural products

## 1 Introduction

5-Hydroxy-1,5-dihydro-2H-pyrrol-2-one [5-hydroxy-1H-pyrrol-2(5H)-one, referred to here for simplicity as  $\gamma$ -hydroxy- $\gamma$ -butyrolactam] containing natural products or pharmaceutically designed compounds represent a large class of structurally diverse molecules exhibiting a wide range of biological activities. Notable examples include: the simplest  $\gamma$ -hydroxy- $\gamma$ -butyrolactam jatropham<sup>2</sup> which displays tumor-inhibitory properties against the P-388 lymphocytic leukemia test system; oteromycin, an antagonist of endothelin receptor and an inhibitor of HIV-1 integrase;<sup>3</sup> the pharmaceutically designed synthetic quinolac<sup>4</sup> (new

potent antimalarial); and the synthetic antitumor agent MT-21<sup>5</sup> (Figure 1). In addition, in the field of synthetic chemistry, the hemiaminal moiety of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams is enabled to undergo various post-functionalizations making these five-membered heterocyclic moieties useful synthetic intermediates particularly in the synthesis of natural products.<sup>6,7</sup> In light of these aspects, many researchers have contributed to the development of synthetic methods to prepare these five-membered-ring heterocycles.<sup>8</sup> This review details methods enabling the synthesis of 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones, classified in three main parts: intramolecular and intermolecular strategies then oxidation processes: synthetic routes to 3-hydroxyisoindolin-1-ones are not included.

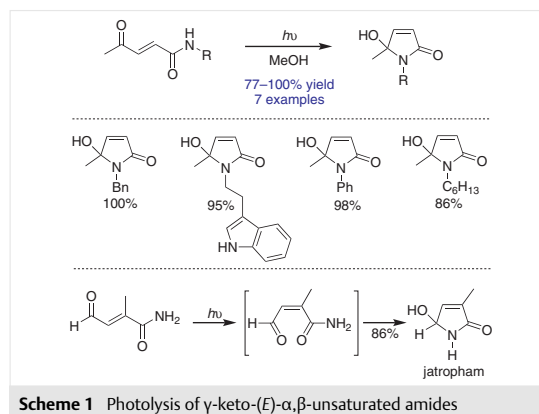


**Figure 1** Representative structures including a  $\gamma$ -hydroxy- $\gamma$ -butyrolactam scaffold

## 2 Intramolecular Route

### 2.1 Photolactamization of $\gamma$ -Keto-(*E*)- $\alpha,\beta$ -unsaturated Amides

As shown in Scheme 1, Dittami and co-workers<sup>9</sup> developed a photocyclization reaction of  $\gamma$ -keto-(*E*)- $\alpha,\beta$ -unsaturated amides to generate  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. The formation of these 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones occurred via an *E* to *Z* isomerization of the C=C bond under irradiation, followed by subsequent lactam formation. The proposed mechanism is supported by the fact that the irradiation of an amide bearing a bulky group (R = *t*-Bu) gave the *Z* isomer instead of the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam. This ketoamide does not undergo subsequent cyclization presumably because steric factors impede the cyclization reaction. Dittami and co-workers<sup>10</sup> then applied this method to the total synthesis of jatropham starting from the corresponding  $\gamma$ -keto- $\alpha,\beta$ -unsaturated amide.



Scheme 1 Photolysis of  $\gamma$ -keto-(*E*)- $\alpha,\beta$ -unsaturated amides

#### Biographical Sketches



**Laurent Commeiras** was born in Marseille (France) in 1975. After studying chemistry at the Paul Cezanne University in Marseille, he received his Ph.D. in 2002 working on the total synthesis of terpenoids isolated from algae of the order

Caulerpales. After a postdoctoral position in the laboratory of Professor Sir Jack E. Baldwin at the University of Oxford (UK), he became Assistant Professor at Aix-Marseille University (France). His main research interests include the total synthe-

sis of natural and biologically active compounds and the development of new methodologies including the formation of hetero-, poly-, and spirocyclic complex structures.



**Jean-Luc Parrain** obtained a Ph.D. in chemistry at the University of Nantes (France) under the supervision of Professor Jean-Paul Quintard. After postdoctoral studies in the laboratory of Professor Steve Davies at Oxford University, he joined the

CNRS as 'chargé de recherche' in the laboratory of Organic Synthesis of the University of Nantes. In 1995, he moved to the University of Marseille and then was appointed a CNRS 'directeur de recherches' in 2001. His research interests include: 1.

new catalytic reactions toward new synthetic methods, development of new organotin, organoboron and silicon reagents; 2. total synthesis of natural compounds, and 3. the functionalization of surfaces.

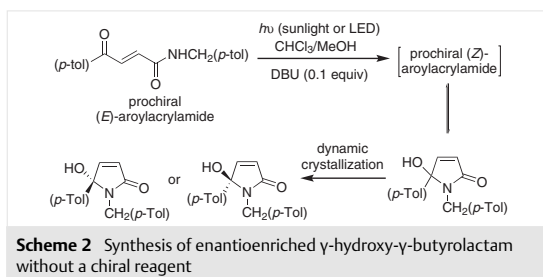


**Muhammad Idham Darusalam Mardjan** was born in Sragen (Indonesia) in 1989. He obtained a B.Sc. in chemistry in 2010 and an M.Sc. in 2012, both at Universitas Gadjah Mada (Indonesia). He received his

Ph.D. in 2016 under the supervision of Dr Laurent Commeiras and Dr Jean-Luc Parrain at Aix-Marseille University (France). In 2014, he became Lecturer at Universitas Gadjah Mada (Indonesia). His main research inter-

ests include photo-induced organic synthesis and application of multicomponent reaction in the synthesis of heterocyclic compounds.

In 2017, the Sakamoto group reported an elegant synthesis of an enantioenriched  $\gamma$ -hydroxy- $\gamma$ -butyrolactam under absolute achiral conditions.<sup>11</sup> This method includes: 1. photochemical isomerization of prochiral (*E*)-aroylacrylamide to prochiral (*Z*)-aroylacrylamide; 2. reversible cyclization reaction to afford a racemic  $\gamma$ -hydroxy- $\gamma$ -butyrolactam; then 3. deracemization via a dynamic crystallization giving optically active  $\gamma$ -hydroxy- $\gamma$ -butyrolactam conglomerates (up to 99% ee) (Scheme 2). It is worth noting that a catalytic amount of a base (DBU) both accelerates the rate of racemization but also the isomerization of the alkenyl group.

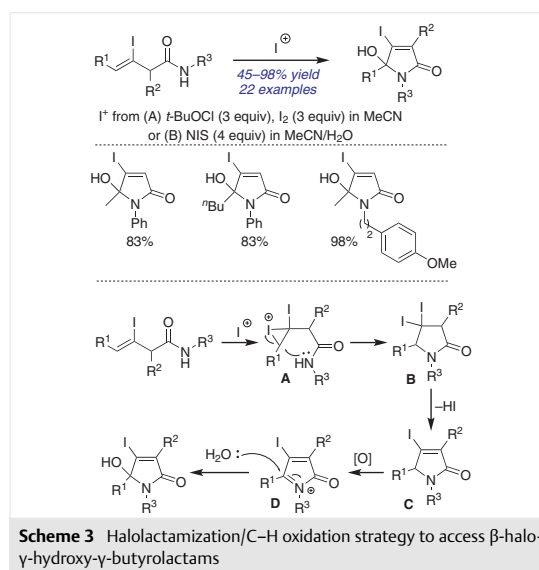


## 2.2 Halolactamization of Enamides, Alkynylamides, and Allenamides

Another synthetic pathway to access  $\gamma$ -hydroxy- $\gamma$ -butyrolactams is the halolactamization of  $\beta,\gamma$ -unsaturated amides such as alk-3-enamides, alk-3-ynylamides, and allenamides (alka-2,3-dienamides).

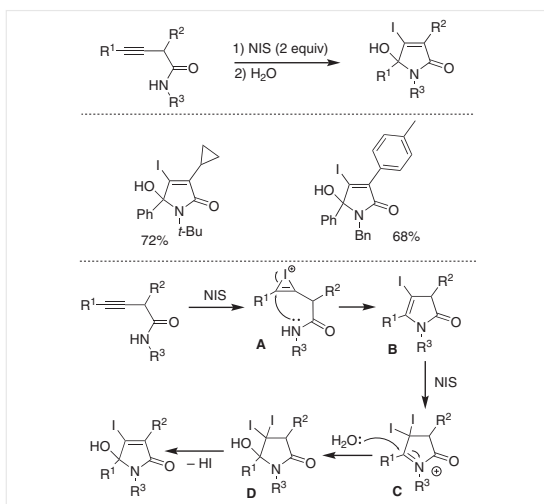
Tang and co-workers<sup>12</sup> carried out a tandem sequence of halolactamization/C–H oxidation of alk-3-enamides to afford  $\beta$ -halo- $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 3). This transformation was mediated by  $\text{BuOCl}/\text{I}_2$  (3 equiv) in commercial MeCN or NIS (4 equiv) in MeCN/ $\text{H}_2\text{O}$  as a source of  $\text{I}^+$ . Under these conditions, the corresponding  $\gamma$ -hydroxy- $\beta$ -iodo- $\gamma$ -butyrolactams were prepared in moderate to high yields with the possibility of post-functionalization thanks to the vinylic carbon–halogen bond. While (*Z*)-iodo-substituted enamides furnished the corresponding  $\gamma$ -hydroxy- $\beta$ -iodo- $\gamma$ -butyrolactams at room temperature, (*Z*)-bromo-substituted enamides (NBS in MeCN/ $\text{H}_2\text{O}$ ) required higher temperatures (50 °C) to prepare  $\beta$ -bromo- $\gamma$ -hydroxy- $\gamma$ -butyrolactams. It should also be noted that the use of either (*E*)-iodo-substituted enamides or non- $\beta$ -halogenated substituted enamide did not furnish the desired  $\beta$ -halo- $\gamma$ -hydroxy- $\gamma$ -butyrolactams. Finally this methodology was extended to *N*-phenethylamines as substrates to obtain pyrroloisoquinoline derivatives in a two-step, one-pot procedure.<sup>13</sup> From a mechanistic point of view, the reaction

between the alk-3-enamide with halogenating reagent ( $\text{I}^+$ ) produces iodonium intermediate **A**, followed by an intramolecular nucleophilic substitution of **A** to give the diiodo-substituted heterocycle **B**. Lactam **C** is then generated by elimination of HI, and it then undergoes allylic oxidation to produce iminium ion **D**, which is trapped by  $\text{H}_2\text{O}$  to give the  $\beta$ -halo- $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 3).

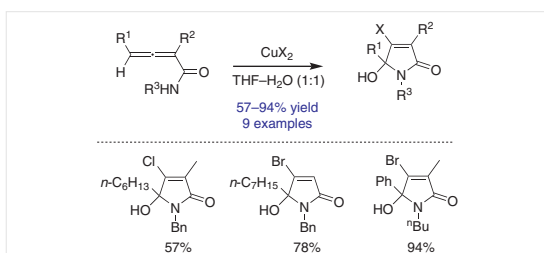


Another route to prepare  $\gamma$ -hydroxy- $\beta$ -iodo- $\gamma$ -butyrolactams (or  $\gamma$ -alkoxy- $\beta$ -iodo- $\gamma$ -butyrolactams) via halolactamization reaction involves alk-3-ynylamides in the presence of 2 equivalents of NIS and an excess of water (or alcohol) (Scheme 4).<sup>14</sup> As a plausible mechanism, Zard and co-workers propose that the treatment of the alk-3-ynylamide with NIS affords the iodonium species **A** which then undergoes cyclization to the cyclic enamide **B**. A second reaction in the presence of NIS produces the iminium intermediate **C** that is trapped with different nucleophiles ( $\text{H}_2\text{O}$ , MeOH, and allyl alcohol) to generate the corresponding lactam **D**; finally, elimination of HI from **D** produces the product.

Based on their previous work on the  $\text{CuX}_2$ -mediated cyclization of allenic acids (alka-2,3-dienoic acids),<sup>15</sup> in 2000 the Ma group reported the synthesis of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams via a halolactamization–hydroxylation reaction of 4-monosubstituted allenamides (Scheme 5).<sup>16</sup> The use of  $\text{CuCl}_2$  or  $\text{CuBr}_2$  in THF/ $\text{H}_2\text{O}$  (1:1) gave diverse  $\beta$ -chloro- or  $\beta$ -bromo- $\gamma$ -hydroxy- $\gamma$ -butyrolactams, respectively, in good yields.



**Scheme 4** Formation of  $\beta$ -halo- $\gamma$ -hydroxy- $\gamma$ -butyrolactams from alk-3-ynamides



**Scheme 5** Formation of  $\beta$ -halo- $\gamma$ -hydroxy- $\gamma$ -butyrolactams from 4-monosubstituted allenamides

In 2005, the Ma group developed a second strategy to prepare  $\gamma$ -hydroxy- $\beta$ -iodo- $\gamma$ -butyrolactams starting from 2- or 4-monosubstituted allenamides, based on a two-step reaction sequence that including an iodolactamization reaction mediated by  $\text{I}_2$ , followed by an oxidation with dioxigen (Scheme 6).<sup>17</sup>

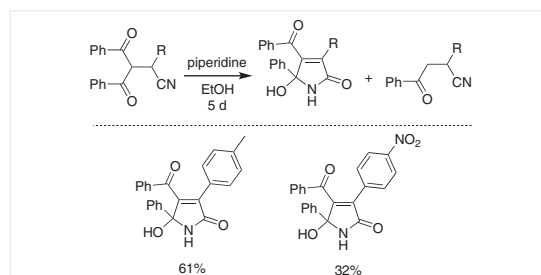


**Scheme 6** Formation of  $\gamma$ -hydroxy- $\beta$ -iodo- $\gamma$ -butyrolactams from 4-monosubstituted allenamides

### 2.3 Cyclization under Basic Conditions

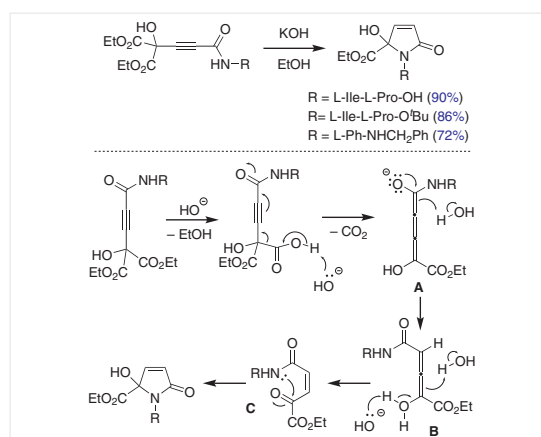
During the synthesis of *N*-benzylidene-furan-2-amine by piperidine-catalyzed cyclization of 3-benzoyl-4-oxo-butanenitrile, Soto and Ciller showed that in the absence of

an aldehyde the reaction gave  $\gamma$ -hydroxy- $\gamma$ -butyrolactams together with 2,4-diaryl-4-oxobutanenitriles, instead of the formation of the furan derivatives (Scheme 7).<sup>18</sup>



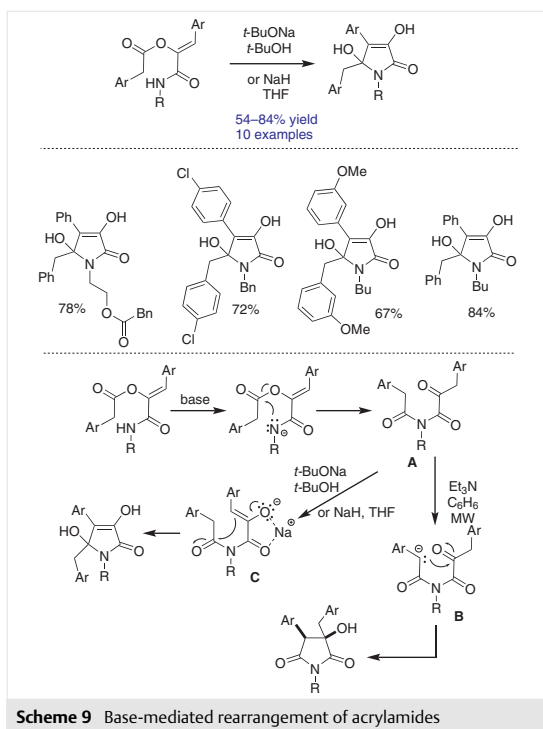
**Scheme 7** Base-catalyzed cyclization of 3-benzoyl-4-oxo-4-phenyl-butanenitriles

In their studies toward the synthesis of cathepsin B inhibitors, Nagao and co-workers exploited a cascade reaction under aqueous basic conditions to prepare L-Ile-L-Pro-OR  $\gamma$ -hydroxy- $\gamma$ -butyrolactams.<sup>19</sup> While L-Ile-L-Pro-OR  $\alpha$ -hydroxy- $\alpha$ -(carbamoyl ethynyl)malonates led to a diastereomixture of  $\gamma$ -hydroxy- $\gamma$ -butyrolactam derivatives in excellent yields (Scheme 8); L-Ph-NHCH<sub>2</sub>Ph  $\alpha$ -hydroxy- $\alpha$ -(carbamoyl ethynyl)malonate diastereoselectively furnished the corresponding  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (72%). The following mechanism is proposed: The reaction cascade starts from alkaline hydrolysis of malonate, followed by a decarboxylation reaction providing cumulenolate intermediate **A**, which under basic conditions transforms into hydroxyallenyl ester **B** and then into ketoamide **C**. Finally, the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam is obtained via intramolecular nucleophilic addition of the amide function onto the ketone.



**Scheme 8** Basic alkyne cascade reaction to access  $\gamma$ -hydroxy- $\gamma$ -butyrolactams

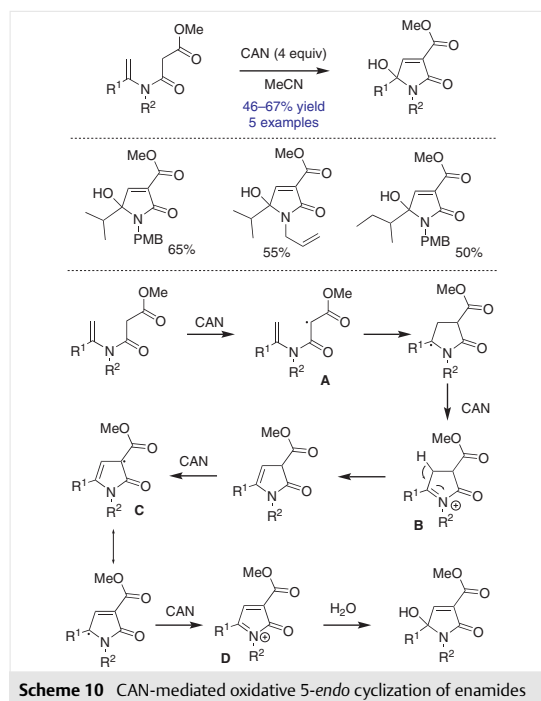
In 2009, the Basso group<sup>20</sup> reported a base-mediated rearrangement of 2-acyloxy-3-arylacrylamides to provide five-membered heterocycles (Scheme 9). Depending on the nature of the base used, weak ( $\text{Et}_3\text{N}$  under microwave heating) vs strong with coordinated counteraction ( $\text{NaH}$ ,  $t\text{-BuOK}$ , or  $\text{LiHMDS}$ ), pyrrolidine-2,5-diones or 1,5-dihydro-2H-pyrrol-2-ones ( $\gamma$ -hydroxy- $\gamma$ -butyrolactams) were selectively prepared. Indeed, mechanistically in the first step, the treatment of 3-aryl-2-acyloxyacrylamide with a base allows the migration of the acyl group onto the amidic nitrogen leading to imide **A**. Interestingly, in a second step, two different scenarios of intramolecular nucleophilic addition can then arise. While the nucleophilic addition of the  $\alpha$ -carbanion of the acetamide (generated with  $\text{Et}_3\text{N}$ ) onto the ketone group of **B** diastereoselectively affords the imide, the nucleophilic addition of the enolate **C**, obtained from strong base with a chelating counteranion, leads to the formation of the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.



## 2.4 Ceric Ammonium Nitrate Mediated Oxidative 5-endo-Cyclization of Enamides

In 2003, Clark and co-workers developed an intramolecular radical strategy to prepare  $\gamma$ -hydroxy- $\gamma$ -butyrolactams starting from enamides (Scheme 10).<sup>21</sup> This process, based on a ceric ammonium nitrate (CAN) mediated oxidative 5-endo cyclization was first developed in methanol to fur-

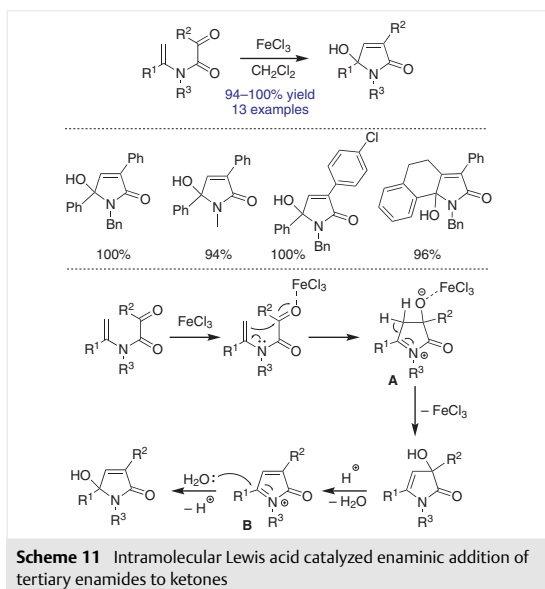
nish  $\gamma$ -methoxy- $\gamma$ -butyrolactams. Switching from MeOH to non-nucleophilic solvent (such as MeCN) followed by an aqueous workup gave  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in good yields. Mechanistically, the reaction between the enamide and the first equivalent of CAN generates the radical intermediate **A** which undergoes 5-endo-trig cyclization followed by a second CAN-assisted oxidation to yield iminium **B**; a  $\beta$ -elimination reaction and a radical generation by the third equivalent of CAN sequence produces **C**. This latter reacts with the last equivalent of oxidant to furnish acyliminium **D**, which upon trapping with water yields the corresponding  $\gamma$ -hydroxy- $\gamma$ -butyrolactam. It is also worth noting that this reaction was selective for 5-endo vs 5-exo and 6-exo cyclization modes ( $\text{R}^2 = \text{allyl}$ ).



## 2.5 Intramolecular Lewis Acid Catalyzed Enaminic Addition of Tertiary Enamides to Ketones

The application of tertiary enamides as nucleophiles in organic synthesis is intriguing since the nucleophilic properties of enamides are relatively low due to the presence of the *N*-acyl group (electron-withdrawing group). Only strong electrophiles have proven their efficacy in such a process. In the preliminary study on the synthesis of clausena alkaloids, Wang and co-workers<sup>22</sup> performed an intramolecular Brønsted acid catalyzed enaminic addition of tertiary enamides to epoxides to prepare dihydropyridinones and pyrrolidinones. These initial results led them to explore

an intramolecular FeCl<sub>3</sub>-catalyzed enaminic addition of tertiary enamides to ketones to form  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 11).<sup>23</sup> This process was found to be general whatever the nature of the substituents; the rate of the reaction depends on the nucleophilicity and the electrophilicity of the enamide and ketone, respectively. For example, the reaction was slower when an *N*-methyl-substituted enamide (R<sup>3</sup> = Me) was used whereas the reaction rate increased when 4-chlorophenyl group (R<sup>2</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>) was installed on the ketone. From a mechanistic point of view, this reaction starts by the activation of the carbonyl by FeCl<sub>3</sub>. This activation enables the enaminic addition of the tertiary enamide to the ketone to generate an iminium intermediate **A**;  $\beta$ -elimination followed by a dehydration reaction forms the iminium ion **B** which finally reacts with water leading to the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.

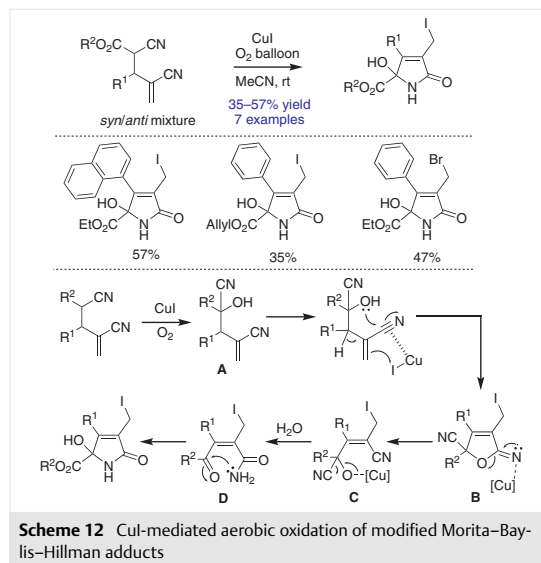


**Scheme 11** Intramolecular Lewis acid catalyzed enaminic addition of tertiary enamides to ketones

## 2.6 CuI-Mediated Aerobic Oxidation of Modified Morita–Baylis–Hillman Adducts

In 2012, Kim and co-workers demonstrated that the modified Morita–Baylis–Hillman adducts were transformed, under aerobic conditions in the presence of a stoichiometric amount of CuI salt, into  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in moderate yields, (Scheme 12).<sup>24</sup> To explain the results, the following mechanism is proposed: Initially, the copper salt mediates the aerobic oxidation (O<sub>2</sub> balloon) of the nitrile derivative to give the cyanohydrin **A**. Then, CuI assists both heterocyclization and iodination of **A** to afford iminolactone **B**. The ketoamide **D** is obtained via ring opening of **B**, hydration of cyanide **C**, then elimination of the nitrile group. Finally, the lactamization step leads to the

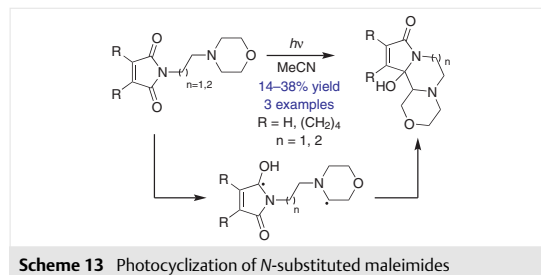
$\gamma$ -hydroxy- $\gamma$ -butyrolactam. It is worth noting that the reaction between nitriles derivatives and CuBr gave the corresponding bromo-substituted lactams, whereas the use of CuCl did not furnish the corresponding chloro-substituted lactams.



**Scheme 12** CuI-mediated aerobic oxidation of modified Morita–Baylis–Hillman adducts

## 2.7 Photocyclization of *N*-Substituted Maleimides

The intramolecular photochemical hydrogen abstraction of *N*-substituted maleimides has also been investigated for the preparation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. During their studies on the synthesis of diazaheterocycles, for the first time in 1983 Coyle and co-workers showed that *N*-[2-(dialkylamino)ethyl]- and *N*-[3-(dialkylamino)propyl]maleimides upon irradiation in MeCN were converted into a diastereomeric mixture of fused piperazine- or diazepine- $\gamma$ -hydroxybutyrolactams, respectively, in moderate yields via a photochemical hydrogen abstraction and cyclization process (Scheme 13).<sup>25</sup> In 1999, Yoon, Mariano, and co-workers explored the nature of the solvent effect on excited state reaction chemoselectivities of the photochemistry of *N*-silylalkyl-substituted maleimides.<sup>26</sup>



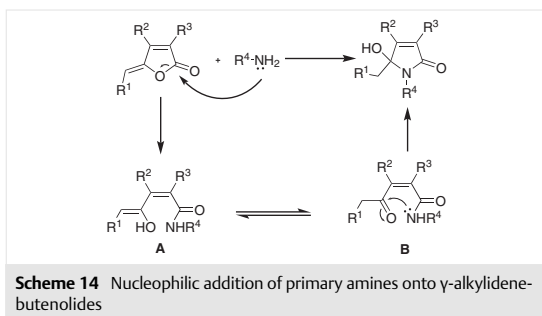
**Scheme 13** Photocyclization of *N*-substituted maleimides



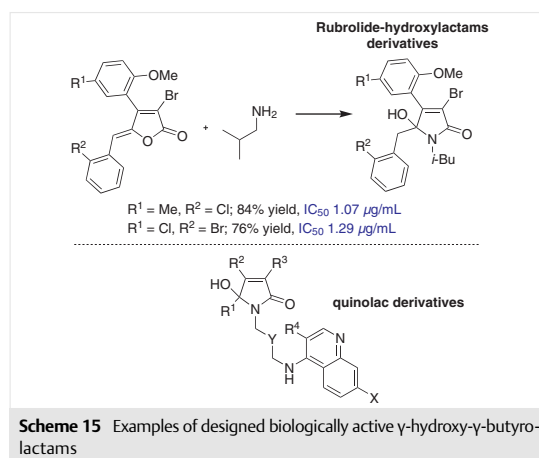
### 3 Intermolecular Route

#### 3.1 Nucleophilic Addition of Primary Amines onto $\gamma$ -Alkylidenebutenolides

Since it was first reported in 1969 by Yamada and co-workers,<sup>27</sup> the most widely utilized method to prepare  $\gamma$ -hydroxy- $\gamma$ -butyrolactams has been the nucleophilic addition of primary amines onto  $\gamma$ -alkylidenebutenolides.<sup>4,28</sup> In this process, enol **A** is first generated and it then readily transforms into the corresponding keto form **B**; an intramolecular nucleophilic addition of amide onto ketone in **B** generates the desired  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 14). In addition, it was shown that the lactamization reaction depends on the nucleophilicity of the primary amines; less nucleophilic amines give (such as aniline) lower yields of the product  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.<sup>28h,i</sup>

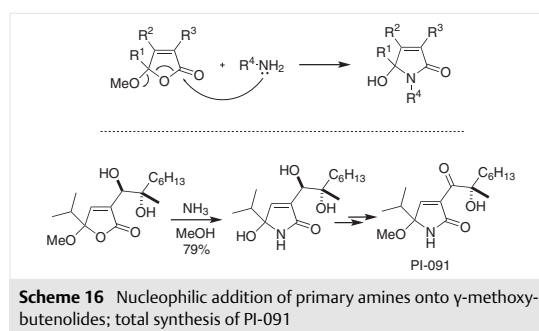


Whatever the nature of the different substituents borne by the  $\gamma$ -alkylidenebutenolide core, the reaction is extremely versatile and provides a convenient and straightforward method for the synthesis of various  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. Some  $\gamma$ -hydroxy- $\gamma$ -butyrolactams synthesized by this route were tested in biological assays (Scheme 15). For instance, Pereira and co-workers prepared several  $\gamma$ -hydroxy- $\gamma$ -butyrolactams derived from rubrolides that display a good antagonist effect against *Enterococcus faecalis* biofilm formation.<sup>28v</sup> Bouillon and co-workers reported the synthesis of fluoroalkylated  $\gamma$ -lactams, named quinolac, derived from 4-aminoquinoline and  $\gamma$ -hydroxy- $\gamma$ -butyrolactam moieties, that display antimalarial properties.<sup>4,28p</sup> It is worth noting that some quinolac derivatives were also obtained from *S*-ethyl  $\gamma$ -keto thioesters using a two-step process or by a one-pot reaction (Scheme 15).<sup>28p,29</sup>



#### 3.2 Nucleophilic Addition of Primary Amines to $\gamma$ -Methoxybutenolides

In a similar fashion, treatment of  $\gamma$ -methoxy- $\gamma$ -butenolides with ammonia gave  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 16).<sup>30</sup> This methodology was elegantly applied for the synthesis of the natural platelet aggregation-inhibition  $\gamma$ -hydroxy-lactam PI-091.<sup>31</sup>

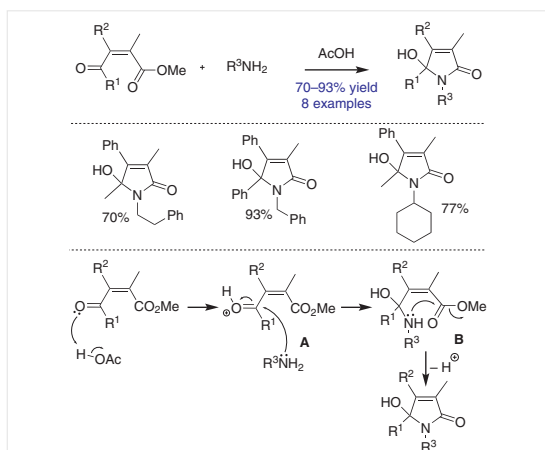


#### 3.3 Reaction between Keto Esters and Primary Amines

Kim and co-workers demonstrated that the treatment of  $\gamma$ -keto- $\alpha,\beta$ -unsaturated esters with primary amines gave  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in good yield (Scheme 17).<sup>32</sup> The limits of the reaction were reached when non-nucleophilic anilines or  $\text{NH}_4\text{OH}$  were used as the starting material. The reaction also failed with cyclohexylamine and methyl 2-methyl-4-oxo-3,4-diphenylbut-2-enoate certainly due to steric hindrance. Mechanistically, the first step is the activation of the carbonyl function by acetic acid. The nucleophilic addition of primary amine onto the activated ketone



**A** produces intermediate **B**. The latter can then cyclize under acidic conditions to afford the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.



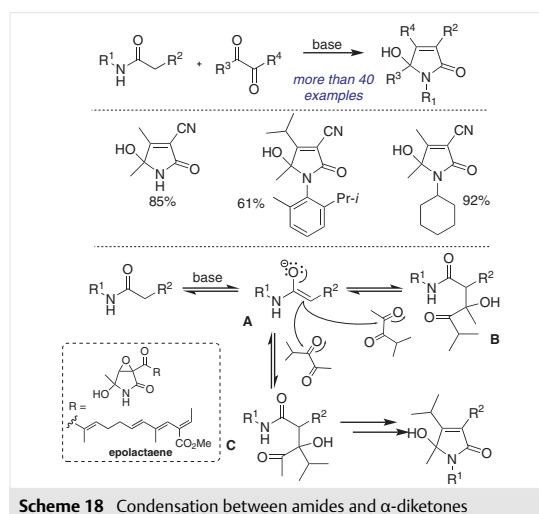
**Scheme 17** Reaction between keto esters and primary amines

### 3.4 Condensation between Amides and $\alpha$ -Diketones

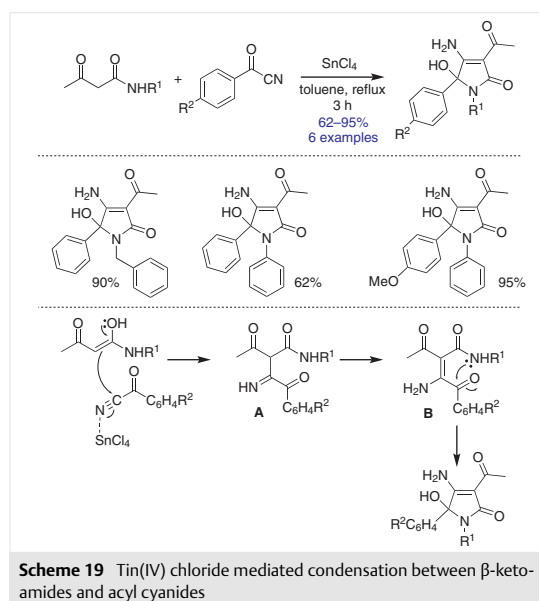
Access to  $\gamma$ -hydroxy- $\gamma$ -butyrolactams has also been achieved via the reaction between amides (possessing an electron-withdrawing group  $R^2$  in the  $\alpha$ -position) and  $\alpha$ -diketones in basic conditions (piperidine, morpholine, or aqueous NaOH) (Scheme 18).<sup>33</sup> When non-symmetrical  $\alpha$ -diketones were used ( $R^3 \neq R^4$ ), the condensation was found to be totally selective. It is postulated that when  $R^3$  is a smaller alkyl group than  $R^4$ , the addition of the enolate **A** occurs on the carbonyl bearing  $R^3$ . However, the second step, which is the nucleophilic addition of the amide onto the remaining carbonyl **B**, is then affected by the steric hindrance of  $R^4$ . If the first step is reversible, the small formed amount of **C** easily leads to the lactam after a cyclization and dehydration sequence. This methodology was applied to the synthesis of 3-substituted 1,5-dihydro-2*H*-pyrrol-2-one derivatives as the core of epolactaene which displays neurotogenic effect on human neuroblastoma cells.<sup>34</sup>

### 3.5 Condensation between $\beta$ -Ketoamides and Acyl Cyanides

Veronese and co-workers showed that the reaction between  $\beta$ -ketoamides and acyl cyanides in the presence of tin(IV) chloride afforded  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 19).<sup>35</sup> While a catalytic amount of tin(IV) chloride afforded  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in low yields (5–30%),



**Scheme 18** Condensation between amides and  $\alpha$ -diketones

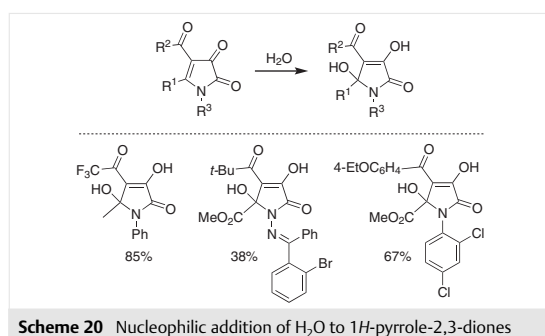


**Scheme 19** Tin(IV) chloride mediated condensation between  $\beta$ -ketoamides and acyl cyanides

the same reaction carried out with a stoichiometric amount gave better isolated yields (60–95%). From a mechanistic point of view, tin(IV)chloride activates the nitrile function followed by a nucleophilic addition of the  $\beta$ -ketoamide giving **A** which then rearranges to **B**. Finally, an intramolecular cyclization affords the corresponding  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.

### 3.6 Nucleophilic Addition of H<sub>2</sub>O and Hydrazides to 1*H*-Pyrrole-2,3-diones

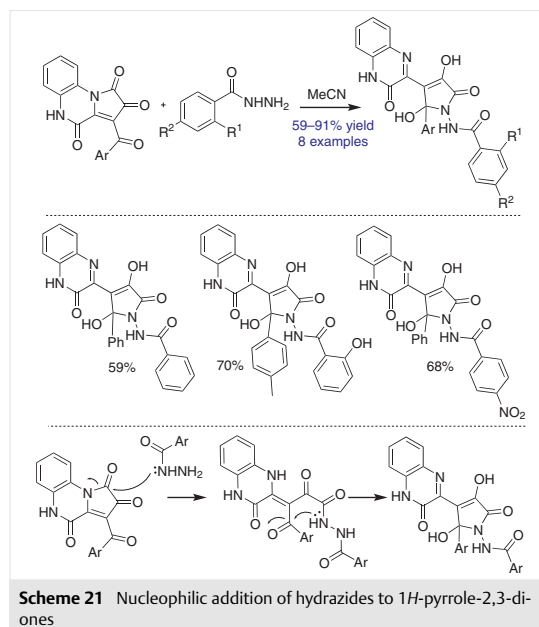
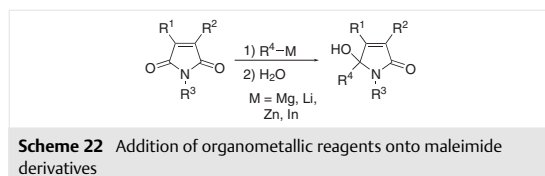
$\gamma$ -Hydroxy- $\gamma$ -butyrolactams were readily synthesized by the nucleophilic addition of H<sub>2</sub>O onto the C-5 position of 1*H*-pyrrole-2,3-diones (Scheme 20),<sup>36</sup> Filyakova and co-workers showed that when bulky substituents (*t*-Bu) were present at C-5, the addition exclusively takes place at C-2 to give the corresponding 4-aminoalk-3-enoic acid derivatives.<sup>36b</sup>



Similarly, Mashevskaya and co-workers showed that addition of the hydrazides onto pyrrolo[1,2-*a*]quinoxaline-1,2,4(5*H*)-trione derivatives furnished the corresponding  $\gamma$ -hydroxy- $\gamma$ -butyrolactams displaying pronounced analgesic activities.<sup>37</sup> From a mechanistic point of view, the addition of hydrazide occurs at C-2 leading to the opened intermediate followed by an intramolecular nucleophilic addition of *N*-amide onto the ketone to give the desired product (Scheme 21).

### 3.7 Addition of Nucleophilic Reagents onto Maleimide Derivatives

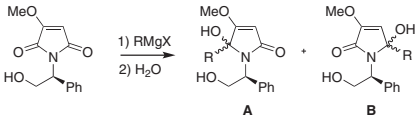
$\gamma$ -Hydroxy- $\gamma$ -butyrolactams were prepared via the addition of carbon nucleophiles onto maleimide carbonyl groups. Generally, reactive organomagnesium<sup>38</sup> reagents were employed in this method. The application of other organolithium<sup>39,40</sup> and weak nucleophilic organozinc<sup>41</sup> reagents has also been reported (Scheme 22).



This methodology was, for example, applied for the synthesis of new  $\gamma$ -hydroxy- $\gamma$ -butyrolactams having a unique Mdm2-Binding mode<sup>42</sup> or for the synthesis of phaeosphaeride **A**.<sup>43</sup> A similar strategy, reported by Coleman and co-workers, involving allylindium species, was also used for the total synthesis of lucilactaene.<sup>7</sup>

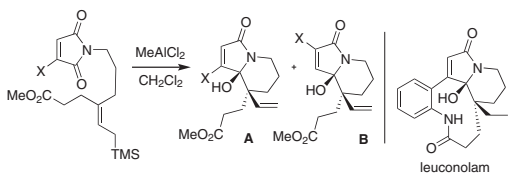
Despite the fact that this method has been extensively applied for the preparation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams, this process suffers from regioselectivity problems when non-symmetric maleimides are employed. In an interesting paper from Huang and co-workers,<sup>38b</sup> the selectivity of the addition of various Grignard reagents onto a 3-methoxymaleimide was examined (Table 1). In general, linear alkyl Grignard reagents selectively gave **A** (ratio **A/B** = 98:2, entry 1). The regioselective addition onto the C-2 carbonyl is due to the presence of a chelation effect with the methoxy group at C-3. In addition, the regioselectivity decreased when more steric demanding nucleophiles were used, as seen by the formation of both **A** and **B**. The use of *i*-BuMgBr and BnMgCl gave both diastereomers with the ratio **A/B** of 88:12 and 63:37 (entries 2 and 3), respectively.

A related strategy involving carbon nucleophilic species was reported by Hoye and co-workers during their studies on the total synthesis of ( $\pm$ )-leuconolam.<sup>44</sup> Indeed, a Lewis acid mediated intramolecular allylsilane addition onto maleimides derivatives was used as the key step. Initially, various Lewis acids were screened as the activator and it was found that MeAlCl<sub>2</sub> facilitated Sakurai-type intramolecular 1,2-addition of allylsilane onto the symmetrical

**Table 1** Regioselective Addition of RMgX onto a 3-Methoxymaleimide


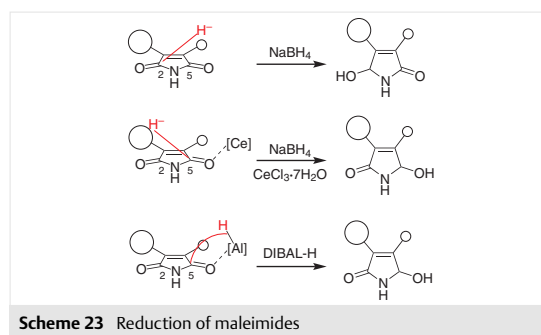
Entry	RMgX	Yield (%)	Ratio A/B
1	<i>n</i> -C <sub>3</sub> H <sub>7</sub> MgBr	78	98:2
2	<i>i</i> -BuMgBr	67	88:12
3	BnMgCl	69	63:37

maleimide to give **A** (X = H) in very good yield (88%) and good diastereoselectivity (dr = 42:1, Table 2, entry 1). Next 2-nitrophenyl- and 2-aminophenyl-substituted maleimides were utilized in this cyclization. 2-Nitrophenyl-substituted maleimides gave exclusively the undesired isomer **B** while 2-aminophenyl-substituted maleimides provided a mixture of the expected isomer **A** and the undesired isomer **B** (entries 2 and 3). The formation of **B** is presumably due to the presence of bulky aromatic substituents. Employing two halogenated maleimide substrates resulted in allylative cyclization of both substrates to give the desired products in good yields and high levels of regio- and diastereoselectivities (entries 4 and 5). It is proposed that the inductive effect of the halogen substituents activates the adjacent carbonyl group allowing allyl addition at the desired position. Additional post-functionalization steps from **A** provided leuconolam.

**Table 2** Lewis Acid Mediated Intramolecular Allylic Silane Addition onto Maleimide Derivatives


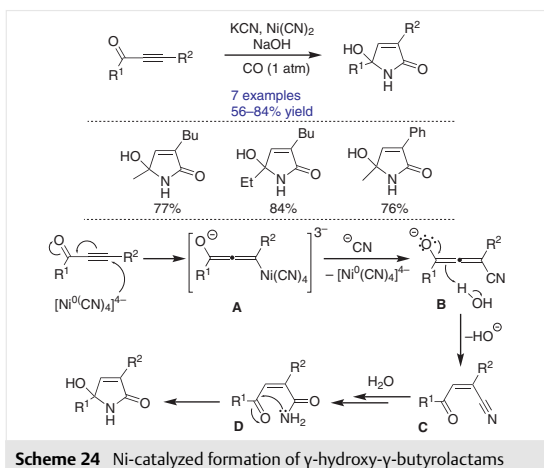
Entry	X	<b>A</b>	<b>B</b>
		Yield (%) (dr)	Yield (%) (dr)
1	H	88 (42:1)	-
2	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	-	85 (15:1)
3	2-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	35 (3:1)	50 (10:1)
4	Br	87 (15:1)	-
5	I	83 (15:1)	-

Hydride reduction (NaBH<sub>4</sub>, NaBH<sub>4</sub>/CeCl<sub>3</sub>·7H<sub>2</sub>O, LiAlH<sub>4</sub>, DIBAL-H, L-Selectride, or LiEt<sub>3</sub>BH) of maleimides is another very commonly used method for the preparation of  $\gamma$ -unsubstituted  $\gamma$ -hydroxy- $\gamma$ -butyrolactams.<sup>45</sup> Compared to the nucleophilic addition of carbon nucleophilic species, the reduction was regioselective and this is ascribed to the depicted models in Scheme 23.<sup>46</sup> In the reduction with sodium borohydride (NaBH<sub>4</sub>), the anion hydride approaches from less hindered C-2, whereas the reduction with NaBH<sub>4</sub>/CeCl<sub>3</sub>·7H<sub>2</sub>O or DIBAL-H gives the other regioisomer. In this case, the regioselectivity is attributed to the complexation of the cerium or aluminum atom with the less hindered carbonyl.

**Scheme 23** Reduction of maleimides

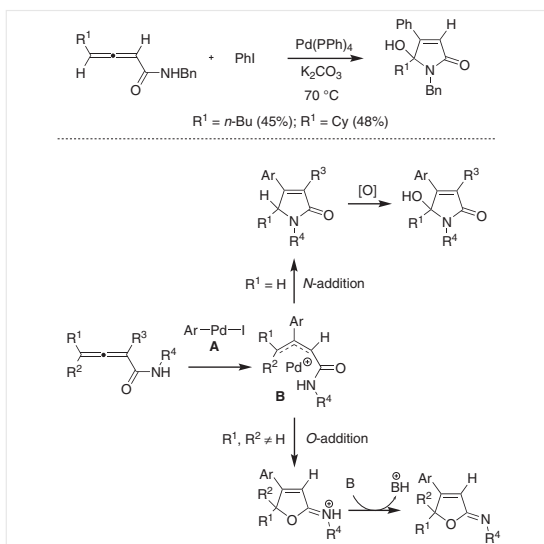
### 3.8 Transition-Metal-Mediated Formation of $\gamma$ -Hydroxy- $\gamma$ -butyrolactams

In their preliminary studies, Arzoumanian and co-workers<sup>47</sup> performed a nickel-catalyzed carbonylation reaction, using [Ni<sup>0</sup>(CO)<sub>3</sub>CN]<sup>-</sup> (prepared in situ from Ni(CN)<sub>2</sub> under basic conditions and CO atmosphere), of alk-1-ynyl ketones to produce  $\gamma$ -hydroxy- $\gamma$ -butyrolactones along with trace amounts of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. It was thought that the formation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams was due to the insertion of the cyanide group instead of CO by an exchange of ligand. Based on these results, the reaction was performed in the presence of excess of potassium cyanide and  $\gamma$ -hydroxy- $\gamma$ -butyrolactams were exclusively obtained (Scheme 24).<sup>48</sup> A study of the scope and limitations showed that increasing the size of the substituent R<sup>1</sup> decreased the yield of the product, while changing the substituent R<sup>2</sup> did not significant effect the yield. The proposed mechanism starts from the addition of [Ni<sup>0</sup>(CN)<sub>4</sub>]<sup>4-</sup> as the active species<sup>49</sup> to the alk-1-ynyl ketone to give complex **A**. After the formation of allenecarbonitrile **B** via cyanide substitution, the **B** undergoes the hydrolysis to afford the amide **D**. Subsequent intramolecular cyclization yields the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 24).



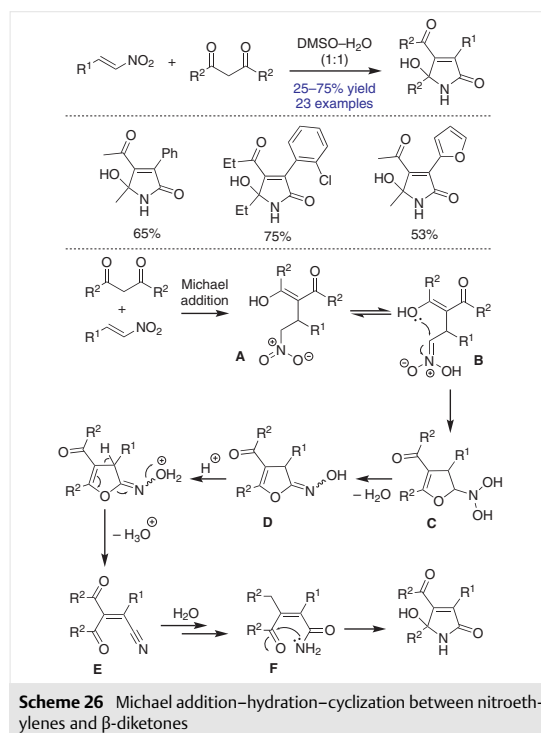
**Scheme 24** Ni-catalyzed formation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams

Following their previous study on the synthesis of lactones from allenic acids via Pd-catalyzed coupling-cyclization reactions,<sup>50</sup> the Ma group<sup>51</sup> extended this route to allenamides that lead to  $\gamma$ -hydroxy- $\gamma$ -butyrolactams or iminolactones. From a mechanistic point of view, the allenamide initially reacts with **A** to yield  $\pi$ -allylpalladium species **B**. Both nitrogen and oxygen atom can serve as nucleophile. The chemoselectivity of this reaction depends on the steric effect at the 4-position of the allenamide. While 4,4-disubstituted allenamides ( $R^1$  and  $R^2 \neq H$ ) furnishes iminolactones via *O*-addition, 4-monosubstituted allenamides ( $R^2 = H$ ) selectively produce  $\gamma$ -hydroxy- $\gamma$ -butyrolactams through *N*-addition (Scheme 25).



### 3.9 Tandem Michael Addition–Hydration–Cyclization between Nitroethylenes and $\beta$ -Diketones

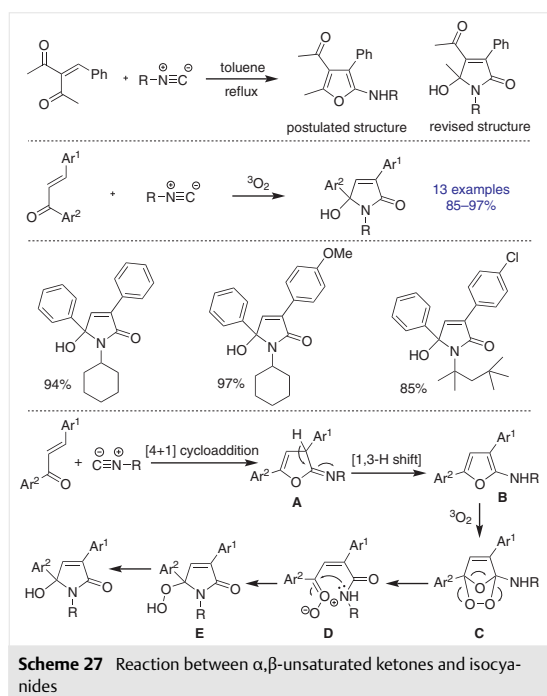
In 2011, Yu and co-workers<sup>52</sup> developed a catalyst-free tandem reaction involving Michael addition, hydration of nitrile, and cyclization in water for the preparation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams from nitroalkenes and 1,3-dicarbonyl compounds (Scheme 26). Regarding the scope of substrates, various nitroalkenes bearing either electron-withdrawing or -donating groups provided  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in moderate to good yields. While the reaction occurred with pentane-2,4-dione and heptane-3,5-dione, the reaction did not occur with other enolate sources such as ethyl acetoacetate, diethyl malonate, and cyclohexane-1,3-dione. From a mechanistic point of view, the reaction between the nitroalkene and  $\beta$ -diketone affords the Michael adduct **A**, which is in equilibrium with the iminium-type ion **B**. The intramolecular nucleophilic addition of the hydroxy group to the iminium-type ion gives **C**, which in turn undergoes dehydration to produce the oxime **D**. The latter is transformed onto the  $\gamma$ -ketonitrile **E** via dehydration. The hydration of nitrile **E** followed with cyclization of amide **F** leads to the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 26).



**Scheme 26** Michael addition–hydration–cyclization between nitroethylenes and  $\beta$ -diketones

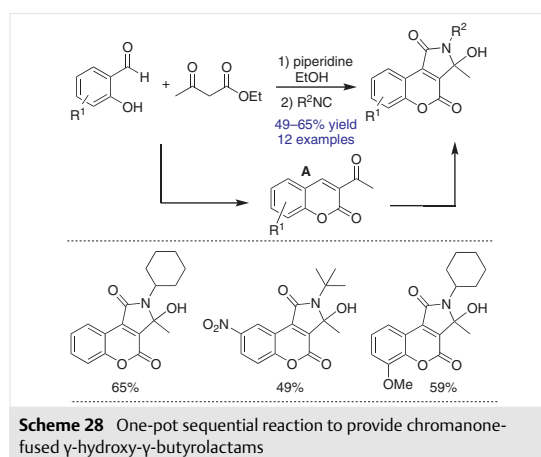
### 3.10 Reaction between $\alpha,\beta$ -Unsaturated Ketones and Isocyanides

In 1997, Yavari and co-workers<sup>53</sup> reported the reaction between  $\alpha,\beta$ -unsaturated ketones and isocyanides to provide a convenient access to 2-aminofurans. However, in 2004 Quai and co-workers,<sup>54</sup> during their studies for the preparation of furans using the same methodology, revised the structure and showed that the product formed is in fact a  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 27). Various  $\alpha,\beta$ -unsaturated ketones, such as chalcone derivatives, and isocyanides were employed in this reaction.<sup>55,56</sup> A plausible mechanism starts with a [4+1]-cycloaddition reaction between the  $\alpha,\beta$ -unsaturated ketone and the isocyanide to afford iminolactone **A**, followed by 1,3-proton shift to generate 2-aminofuran **B**. The reaction of **B** and triplet oxygen then generates ozonide **C**. Fragmentation of **C**, followed by cyclization of **D** provides hydroperoxide **E**, which undergoes disproportionation to furnish the final  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.

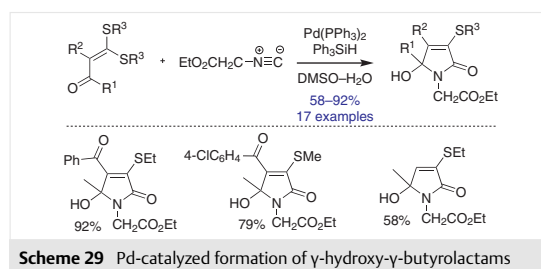


Ghandi and co-workers<sup>57</sup> applied this method to the preparation of chromanone-fused  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in good yields whatever the nature of substituents by a one-pot sequential reaction that included piperidine-catalyzed condensation between salicylaldehyde derivatives and ethyl acetoacetate to form  $\alpha,\beta$ -unsaturated ketones **A** followed by the addition of an equimolar amount

of isocyanide (Scheme 28). Dallinger and co-workers showed that the outcome of this reaction depends on the reaction conditions. While chromanone-fused  $\gamma$ -hydroxy- $\gamma$ -butyrolactams were obtained in a standard open vessel, 5-hydroxy-2-iminofuran-fused coumarins were synthesized in a closed vessel.<sup>58</sup>



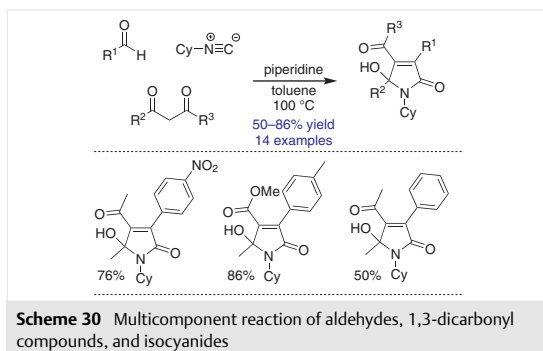
In 2016, Wang and co-workers<sup>59</sup> described a new route to  $\gamma$ -hydroxy- $\gamma$ -butyrolactams starting from ketene dithioacetals and isocyanides involving a Pd-catalyzed C–S bond activation/isocyanide insertion/hydrogenation/aerobic oxidation/intramolecular nucleophilic addition. This reaction was general whatever the nature of the substituents on the ketene dithioacetal (Scheme 29).



### 3.11 Multicomponent Reaction

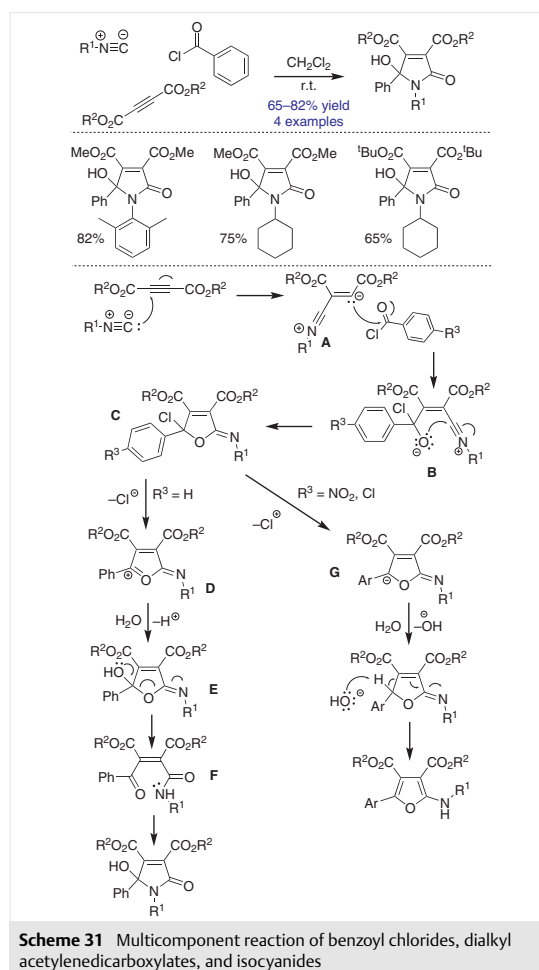
Liang and co-workers<sup>60</sup> took the advantage of the transformation of  $\alpha,\beta$ -unsaturated ketones and cyclohexyl isocyanide to  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 27) to carry out a three-component reaction involving aldehydes, 1,3-dicarbonyl compounds, and isocyanides. Under the reaction conditions, intermediate  $\alpha,\beta$ -unsaturated ketones were generated in situ and these reacted with the isocyanide to give  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in good yields (Scheme 30). Various aromatic and aliphatic aldehydes were used

successfully; electron-deficient aldehydes gave higher yields than electron-rich aldehydes. The limitations of the reaction were reached when diethyl malonate and 2-cyanoacetate were used as the substrates.

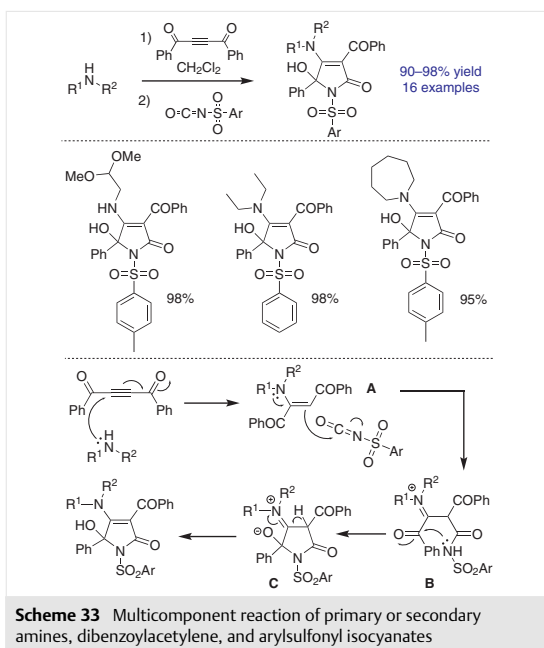
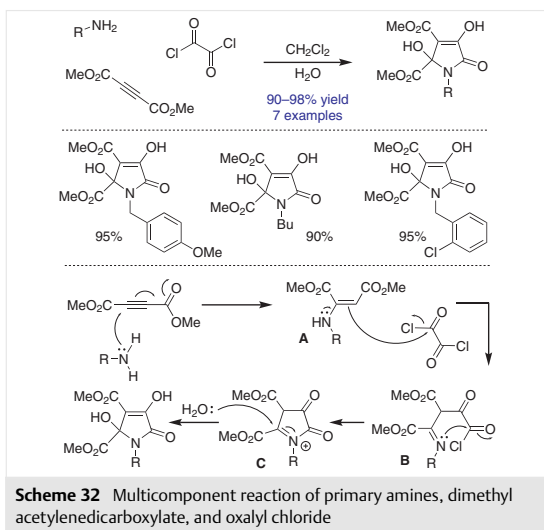


Yavari and co-workers<sup>61</sup> reported another multicomponent reaction to access  $\gamma$ -hydroxy- $\gamma$ -butyrolactams from isocyanides, dialkyl acetylenedicarboxylates, and benzoyl chlorides (Scheme 31). From a mechanistic point of view, the zwitterion **A** is generated from the addition of the isocyanide onto the acetylenedicarboxylate; **A** reacts with benzoyl chloride to form the intermediate **B** which undergoes 5-*exo*-dig cyclization to afford **C**. Iminolactone **C** has two different reactivities depending on the nature of the substituents on the benzoyl chloride. When benzoyl chloride ( $R^3 = H$ ) was used as the substrate, elimination of the chloride anion occurs to give intermediate **D** and subsequent addition of water onto the oxonium species provides iminolactone **E**. The latter is transformed into the corresponding open form intermediate **F**, which subsequently undergoes recyclization to produce the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam. On the other hand, the presence of an electron-withdrawing group in the *para* position of benzoyl chloride ( $R^3 = Cl, NO_2$ ) favors the formation of the anion **G** which gives an aminofuran.

As an extension, Yavari and co-workers developed a multicomponent reaction involving primary amines, dimethyl acetylenedicarboxylate, and oxalyl chloride to produce  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 32).<sup>62</sup> The reaction is initiated by the nucleophilic 1,4-addition of the primary amine onto dimethyl acetylenedicarboxylate to furnish the enamine **A** which then undergoes addition to oxalyl chloride to generate **B**. Intramolecular cyclization of **B** followed by the addition of water onto the acyliminium moiety of **C** leads to the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.

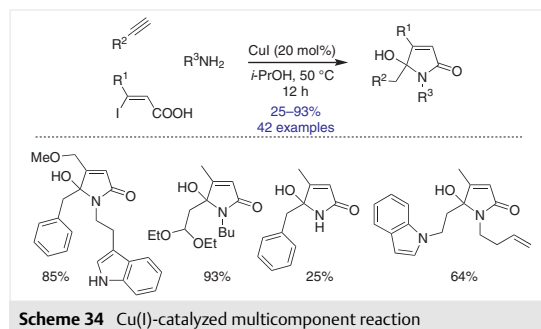


Alizadeh and co-workers developed another example of a multicomponent reaction initiated by a Michael addition to produce  $\gamma$ -hydroxy- $\gamma$ -butyrolactams from primary<sup>63</sup> or secondary amines,<sup>64</sup> dibenzoylacetylene, and arylsulfonyl isocyanates under neutral conditions. It is proposed that the process starts by the formation of enamines **A** via the nucleophilic addition of the amine onto dibenzoylacetylene. Enamine **A** then undergoes addition to the carbonyl moiety of the arylsulfonyl isocyanate to generate intermediate **B**. An intramolecular cyclization of **B** followed by  $\beta$ -elimination and protonation of alkoxide **C** finally produces the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 33).



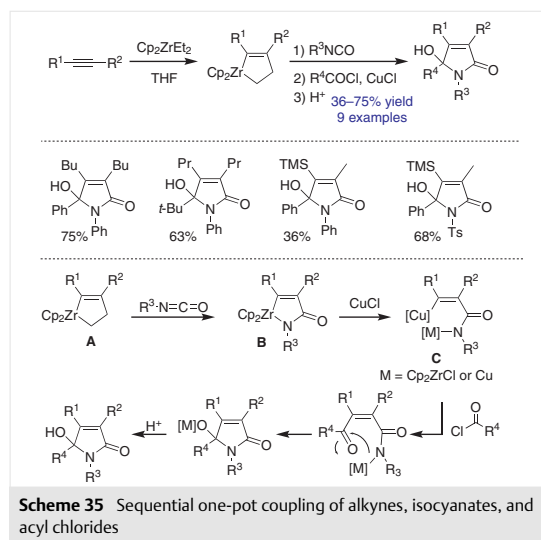
In 2016, Commeiras and co-workers developed the copper-catalyzed multicomponent reaction between primary amines, terminal alkynes, and (*Z*)-3-iodoacrylic acids to smoothly access a library of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams.<sup>65</sup> This reaction is based on a cascade in which three individual steps (palladium-free Sonogashira enyne coupling/heterocyclization/ $\gamma$ -hydroxylactam formation) are combined in a synthetic process (Scheme 34). It is worth noting that

this process was applied to the synthesis of potentially biologically active indolo-lactam derivatives.<sup>66</sup> The limitation of the reaction was reached when less nucleophilic amines, such as aniline, were used.



### 3.12 Sequential One-Pot Coupling of Alkynes, Isocyanates, and Acyl Chlorides

Takahashi and co-workers reported a zirconium-mediated sequential one-pot coupling reaction of alkynes, isocyanates, and acyl chlorides to access  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 35).<sup>67</sup> The reaction occurred with both symmetrical and unsymmetrical alkynes to regioselectively afford a single isomer. Diverse isocyanates and sterically hindered acyl chlorides were used without affecting the isolated yields. Mechanistically, the alkyne first reacts with  $\text{Cp}_2\text{ZrEt}_2$  to give the zirconacyclopentene intermediate **A** which reacts with the isocyanate to furnish the oxazirconacycle **B**. Then, transmetalation of **B** with copper(I) chloride furnishes copper intermediate **C**. Reaction of **C** with acyl



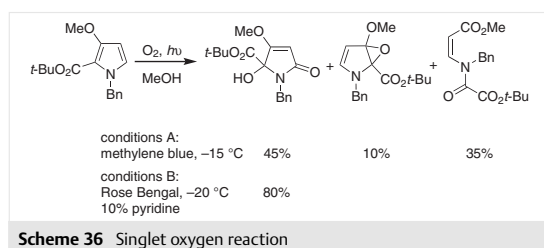


chloride followed by intramolecular nucleophilic addition of nitrogen to the carbonyl group then hydrolysis furnishes the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 35).

## 4 Oxidation of Heterocyclic Compounds

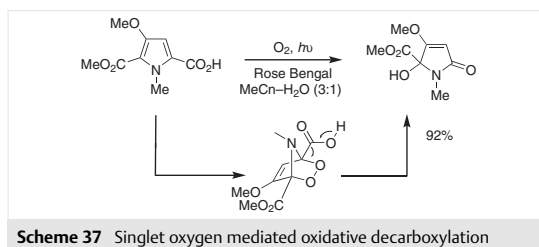
### 4.1 Oxidation of Pyrroles

Since the first report of the photochemical oxidation of pyrrole in 1912,<sup>68</sup> it was only after the work of De Mayo and Reid in 1962 that the structure of the unidentified crystalline products was elucidated and proved to be a  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.<sup>69</sup> From this date, the dye-sensitized photooxygenation of pyrroles in the presence of sensitizer such as methylene blue, Rose Bengal, tetraphenylporphyrin, as well as 9,10-dicyanoanthracene has been the subject of extensive investigation. However, it was shown that this reaction has low chemoselectivity and furnishes a complex mixture of oxygenated products rising from decomposition of hydroperoxides, dioxetanes, or endoperoxides.<sup>70</sup> Nevertheless, the yields of isolated  $\gamma$ -hydroxy- $\gamma$ -butyrolactams remain low and the synthetic utility of this methodology is limited. However, Wasserman and co-workers<sup>71</sup> demonstrated that when the reaction was performed with a pyrrole bearing both an electron-withdrawing group ( $\text{CO}_2t\text{-Bu}$ ) at C-2 and an electron-donating group (OMe) at C-3, the photooxygenation mainly furnished the corresponding  $\gamma$ -hydroxy- $\gamma$ -butyrolactam in 45% yield as a mixture with two other products (Scheme 36). Interestingly, it was also shown that the addition of a proton acceptor, such as pyridine, enhanced the yield of the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam up to 80%.

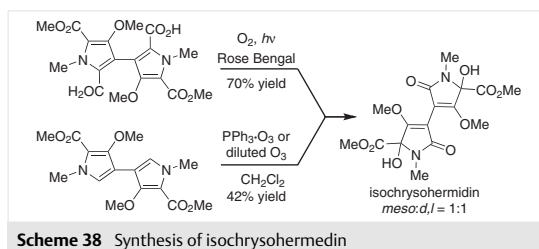


In parallel, Boger and Baldino developed a singlet oxygen photooxidation followed by a subsequent oxidative decarboxylation to access similar structures in good yield (92%) without observing the formation of polyoxygenated byproducts (Scheme 37).<sup>72</sup>

This process was nicely applied to the synthesis of *dl*- and *meso*-isochrysohermidin<sup>73</sup> as well as isochrysohermidin-distamycin hybrids.<sup>74</sup> It is worth mentioning that a mixture of triphenylphosphine and ozone, or with only di-

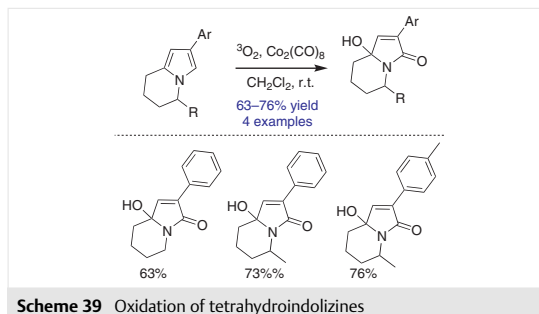


luted ozone in dichloromethane, was also useful for the oxidation of pyrroles.<sup>73,75</sup> This is potentially an alternative process for the synthesis of isochrysohermidin starting from the corresponding bis-pyrrole without a carboxylic acid function (Scheme 38).

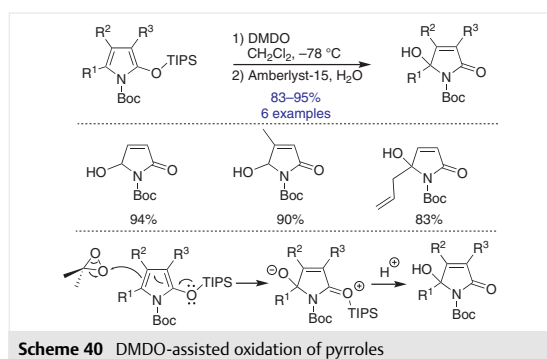


In 2016, Smith, Bissember, and co-workers developed a simple and cost-effective reactor to photooxidize *N*-substituted pyrroles in the presence of base (NaOAc), oxygen, and ethanol to afford a mixture of  $\gamma$ -hydroxy- and  $\gamma$ -alkoxy- $\gamma$ -butyrolactams in good yields.<sup>76</sup>

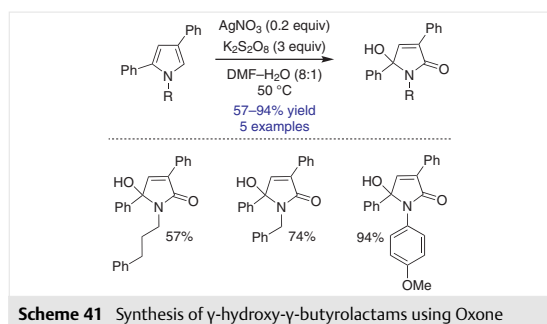
In 1995, Wang and Alper reported that dicobalt octacarbonyl complex  $[\text{Co}_2(\text{CO})_8]$  in the presence of triplet oxygen oxidized tetrahydroindolizines to  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in good yields with total chemoselectivity (Scheme 39). A similar oxidation also occurred with singlet oxygen.<sup>77</sup> Related chemoselectivity was also observed when 2,3-dihydro-1*H*-pyrrolizine derivatives<sup>78</sup> and 4,5,6,7-tetrahydro-1*H*-indole backbones<sup>79</sup> were subjected to singlet oxygen.



As an alternative to using oxygen as the oxidant, Boukouvalas and co-workers used dimethyldioxirane to regio- and chemoselectively transform 2-siloxyppyroles into  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in excellent yields (Scheme 40).<sup>80</sup>

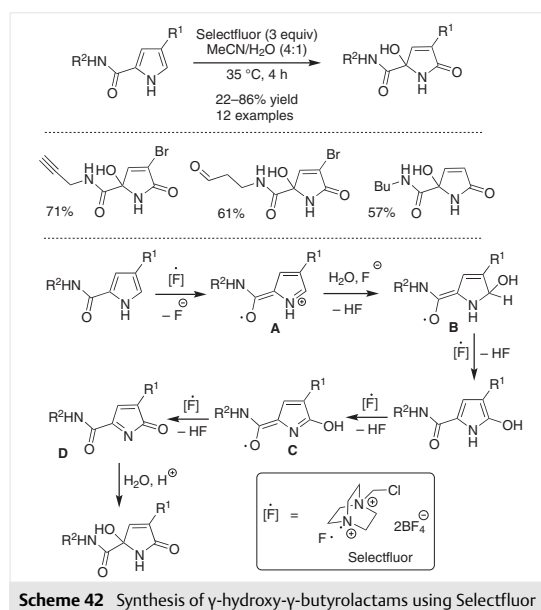


While investigating the synthesis of pyrrole-2-phosphonate derivatives via an oxidative phosphorylation of pyrroles with diethyl phosphite in the presence of a catalytic amount of  $\text{AgNO}_3$  and 3 equivalents of Oxone, Kim and co-workers found that in the absence of diethyl phosphite,  $\gamma$ -hydroxy- $\gamma$ -butyrolactams were smoothly prepared (Scheme 41).<sup>81</sup>



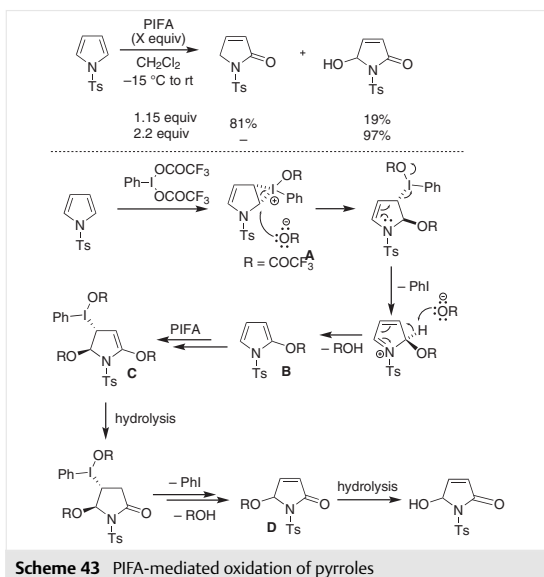
During their studies on the fluorination of pyrrole-2-carboxylic acid derivatives, Troegel and Lindel observed that the use of excess Selectfluor (3 equiv) produced  $\gamma$ -hydroxy- $\gamma$ -butyrolactam byproducts.<sup>82</sup> Taking advantage of this reactivity, an efficient Selectfluor-mediated single electron transfer oxidation of pyrrolocarboxamides in water was developed for the preparation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. This methodology was compatible with several sensitive functional groups and the lactams were prepared in up to 86% yield (Scheme 42).<sup>83</sup> From a mechanistic point of view, Selectfluor is expected to act as a single-electron transfer oxidant. The first step is a one-electron oxidation of pyrrole affording the radical iminium **A**. Next, nucleophilic addition of water to the iminium ion followed by abstraction of a hydrogen radical by Selectfluor affords 5-hy-

droxypyrrrole **B**. Further one-electron oxidation initially produces **C** then **D**. The final step is the nucleophilic addition of water to **D** to furnish the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.

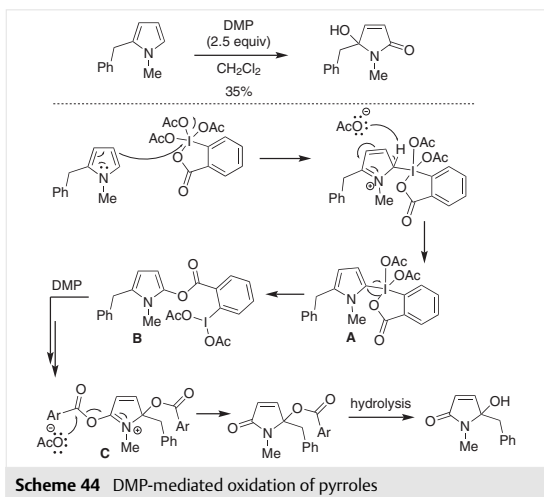


Hypervalent-iodine-assisted oxidative dearomatization of pyrroles is another method to prepare  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. In 2010, Şentürk and co-workers carried out the controlled oxidation of *N*-tosylpyrroles with [bis(trifluoroacetoxy)iodo]benzene (PIFA). The use of 1.15 equivalents of PIFA produced both lactams and  $\gamma$ -hydroxy- $\gamma$ -butyrolactams in 81% and 19% yields, respectively. Increasing the quantity of PIFA to 2.2 equivalents gave the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam as the sole product in 97% yield (Scheme 43).<sup>84</sup> Mechanistically, pyrrole reacts with PIFA to give iodonium ion **A**. The latter undergoes nucleophilic substitution with the trifluoroacetate ion followed by elimination of phenyl iodide and aromatization to give **B**. Reaction with a second equivalent of PIFA leads to the formation of **C**, which after hydrolysis and subsequent elimination produces acyloxyppyrrrole **D**. Finally, further hydrolysis of **D** furnishes the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.

In 2013, Smith and co-workers used the Dess–Martin periodinane in the controlled oxidation of pyrroles to access  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. While unsubstituted pyrroles were transformed into  $\gamma$ -aroyloxy- $\gamma$ -butyrolactams, 2-substituted pyrroles gave the sensitive  $\gamma$ -hydroxy- $\gamma$ -butyrolactam in fair yield (35%) (Scheme 44).<sup>85</sup> Similar results were obtained starting from 2,3,4-trisubstituted pyrroles.<sup>86</sup> From a mechanistic point of view, it is proposed that the electrophilic aromatic substitution of pyrrole onto the DMP iodine, followed with elimination of a proton affords intermediate



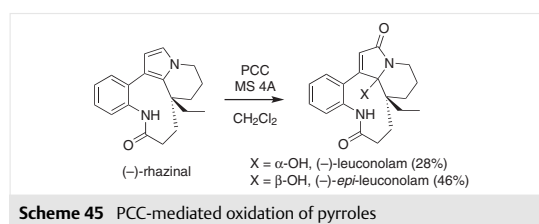
**A.** Then, migration of the C-2 benzoate oxygen of the pyrrole produces **B**. The more reactive intermediate **B** undergoes a second reaction with DMP and migration to give **C**. The latter is initially subjected to a transesterification, followed by hydrolysis to produce the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.



In the course of their enantioselective total synthesis of (-)-rhazinal, (-)-rhazinilam, (-)-leuconolam, and (+)-epileuconolam, Banwell and co-workers employed pyridinium chlorochromate in the oxidation of the pyrrole moiety.

Upon treatment of (-)-rhazinal with PCC, both (-)-leuconolam (28%) and (+)-epileuconolam (46%) were obtained as a separable mixture (Scheme 45).<sup>87</sup>

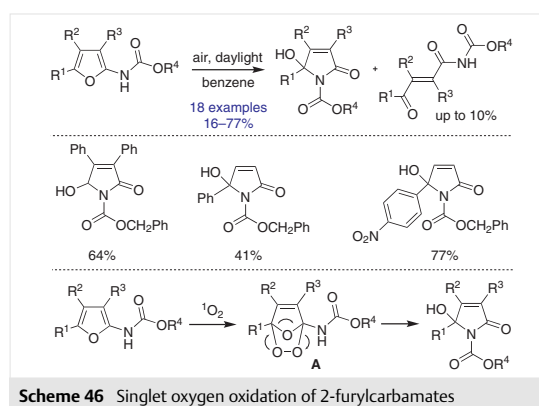
Finally, synthesis of  $\gamma$ -hydroxy- $\gamma$ -butyrolactam moieties from pyrrole was also observed with the use lead tetraacetate.<sup>88</sup>



## 4.2 Oxidation of Furans

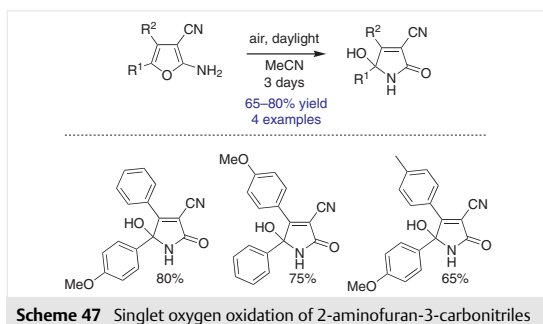
Whereas the photooxidation of pyrroles potentially suffers from chemoselectivity problems, similar strategies starting from furan can offer an alternative.

The ring transformation of 2-furylcarbamates with singlet oxygen mainly furnished  $\gamma$ -hydroxy- $\gamma$ -butyrolactams together with up to 10% of *trans*-ketoamides (Scheme 46).<sup>89</sup> The formation of hydroxylactams is explained via the formation of endoperoxides **A** that undergo cleavage and loss of an oxygen to produce *cis*-ketoamides, which undergo either cyclization to form  $\gamma$ -hydroxy- $\gamma$ -butyrolactams or isomerization to furnish *trans*-ketoamides. Further irradiation of the *trans*-ketoamide side products allowed isomerization of the double bond followed by spontaneous cyclization to form  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. This process has been also used for the synthesis of 5-hydroxy-5-( $\beta$ -D-ribofuranosyl)-1,5-dihydro-2H-pyrrol-2-one.<sup>90</sup>



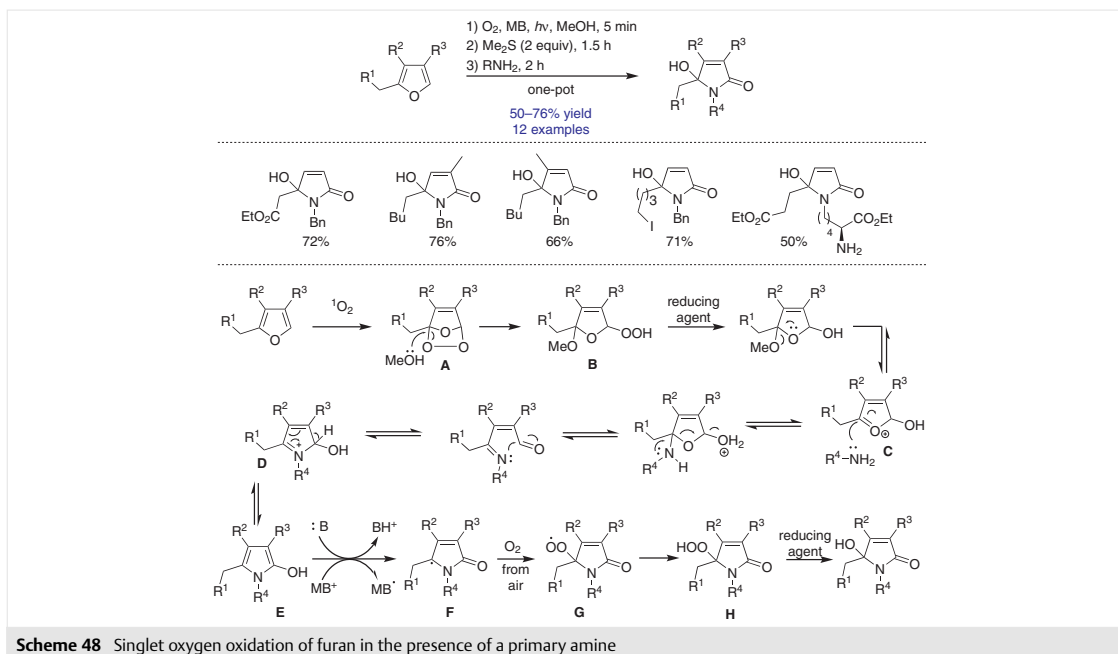
In related a strategy, Soto and co-workers<sup>91</sup> demonstrated that the exposure of 2-aminofuran-3-carbonitriles to singlet oxygen led to the formation of  $\gamma$ -hydroxy- $\gamma$ -butyro-

lactams (Scheme 47). The limit of the reaction is reached when R<sup>2</sup> is an electron-withdrawing group such as 4-chlorophenyl.

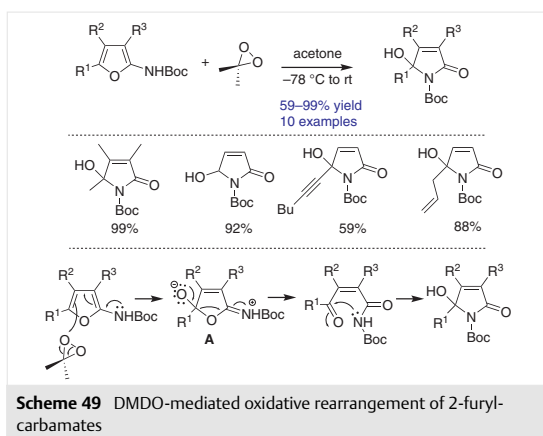


The Vassilikogiannakis group made a notable development for the synthesis of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams via singlet oxygen mediated oxidation of furans. The treatment of substituted furans with singlet oxygen ( $^1\text{O}_2$ ) in the presence of Rose Bengal as photosensitizer, reducing agent (such as Me<sub>2</sub>S), and primary amines afforded 1,3-dihydro-2*H*-pyrrol-2-ones, a key intermediate to access nitrogen-containing polycyclic compounds.<sup>92</sup> They also took the advantage of photosensitizer activity and catalytic redox ca-

pability of methylene blue (MB) to prepare  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 48).<sup>93</sup> This sequence was performed with differently substituted furans, primary amines, as well as ammonia. Various  $\gamma$ -hydroxy- $\gamma$ -butyrolactams bearing alkyl, halogen, alkene, ketone, and ester functions were produced in moderate to high yields. Only  $\alpha$ -branched primary amines are not suitable reactants, certainly due to steric reasons. From a mechanistic point of view, the synthesis is initiated by the reaction between furan and singlet oxygen (generated in the presence of methylene blue photosensitizer under the irradiation of visible light) in methanol to give the hydroperoxide **B** via the intermediate **A**. The reducing agent reduces the peroxide to give oxonium ion **C** via the elimination of a methoxy group. The transformation of oxonium ion **C** into iminium ion **D** occurs via the cascade: 1. addition of primary amine, 2. ring opening, and 3. cyclization. The aromatization of **D** produces 2-hydroxypyrrole **E**, which is the tautomer of a 1,3-dihydro-2*H*-pyrrol-2-one. The intermediate **E** then undergoes to both protonation of base (B) and electron transfer to methylene blue to produce the captodative radical **F**, which is trapped with oxygen from air to furnish another radical species **G**. The latter is transformed onto peroxide **H** via hydrogen radical transfer. Finally, the reduction of peroxide **H** produces the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam.



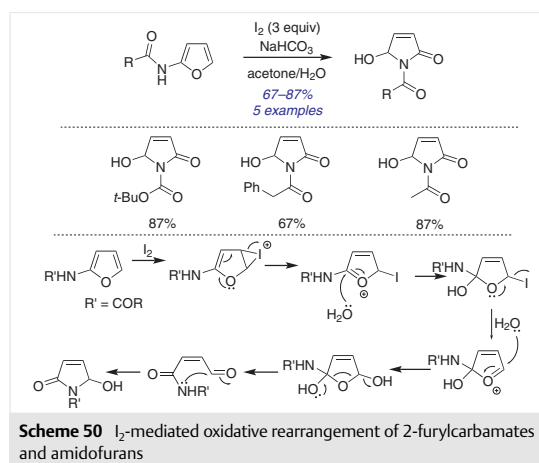
In an expansion of their work on the dimethyldioxirane-mediated oxidation of heterocyclic compounds,<sup>80</sup> Boukouvalas and co-workers reported a mild, general and efficient oxidative rearrangement of 2-furylcarbamates for the preparation of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams<sup>94</sup> with excellent regio- and chemoselectivity (Scheme 49). Mechanistically, reaction between 2-furylcarbamate and DMDO gives intermediate **A**, which undergoes ring opening and intramolecular nucleophilic addition to produce the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam. It is important to note that  $\gamma$ -hydroxy- $\gamma$ -butyrolactams can be generated from this reaction even though the electron-donating ability of 2-furylcarbamates is lower than that of 2-siloxypyrroles (Scheme 40).<sup>95</sup>



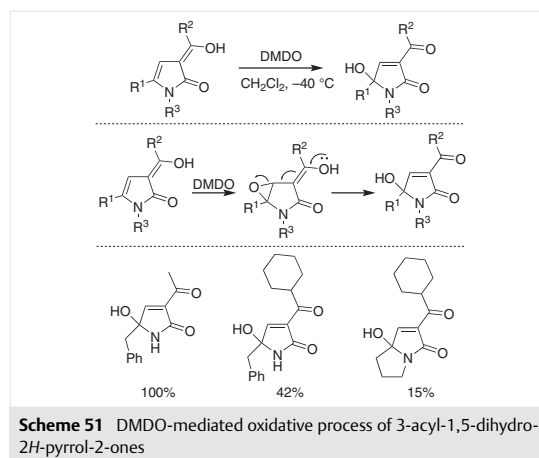
During their studies towards the total synthesis of longeracinyllin A, a Daphniphyllum alkaloid, Padwa and co-workers utilized an iodine-mediated oxidative rearrangement of 2-furylcarbamates to prepare  $\gamma$ -hydroxy- $\gamma$ -butyrolactams.<sup>96</sup> Indeed, on attempted deprotection of the 1,3-dithiane moiety with iodine in a basic aqueous medium, 2-furylcarbamates gave  $\gamma$ -hydroxy- $\gamma$ -butyrolactams via a mechanism similar to the aza-Achmatowicz oxidation (Scheme 50). This process was found to be also efficient starting from amidofurans.

### 4.3 Oxidation of 3-Acyl-1,5-dihydro-2H-pyrrol-2-ones

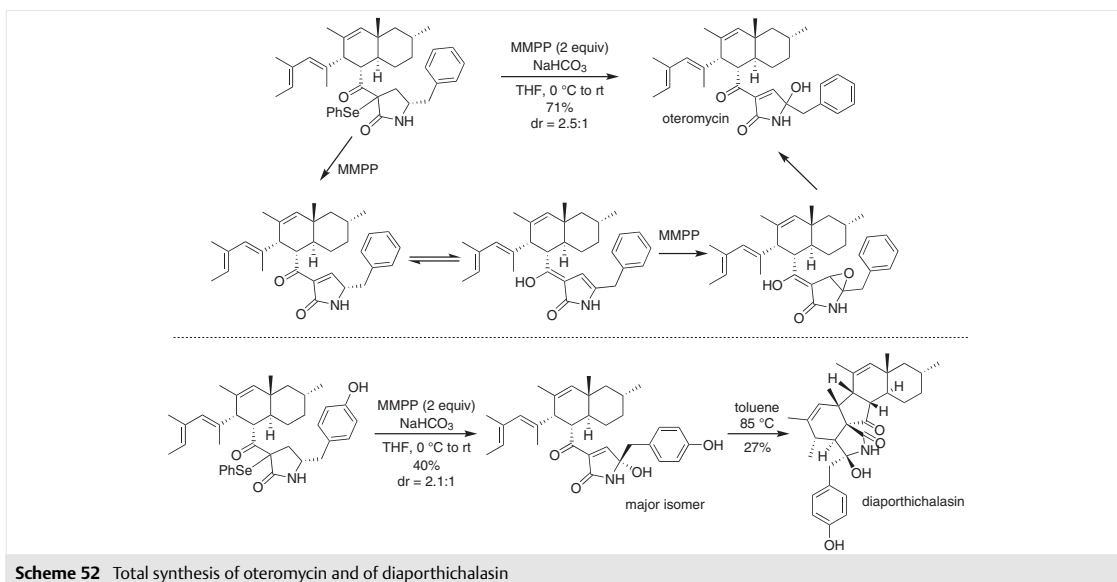
An access to 3-acyl-5-hydroxy-1,5-dihydro-2H-pyrrol-2-one by the DMDO-mediated oxidation of 3-acyl-1,5-dihydro-2H-pyrrol-2-one was initially developed by Snider and Neubert (Scheme 51).<sup>97</sup> This process which starts by the epoxidation of the endocyclic double bond followed with ring opening of the epoxide, was also applied to the synthesis of ring system of several natural products such as



oteromycin, epolactaene, fusarin C, as well as UCS1025A. However, the low yield observed is probably due to the relative instability of the  $\alpha$ -acyl- $\gamma$ -butyrolactams.

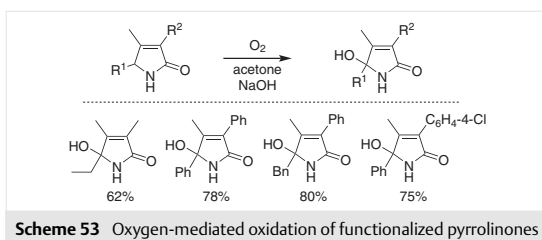


This process was extended by Uchiro and co-workers to the total synthesis of oteromycin<sup>98</sup> in a one-pot four-step sequence that included: 1. oxidative/elimination of selenolactam, 2. epoxidation an endocyclic double bond, then 3. ring opening of the epoxide. Whereas dimethyldioxirane and 3-chloroperoxybenzoic acid furnished a complex mixture of products, magnesium monoperoxyphthalate (MMPP) successfully afforded the desired  $\gamma$ -hydroxy- $\gamma$ -butyrolactam in 71% yield as a mixture of diastereomers (dr = 2.5:1, Scheme 52). This strategy was also applied to the total synthesis of diaporthichalasin.<sup>99</sup>



#### 4.4 Oxidation of 1,5-Dihydro-2H-pyrrol-2-ones

Oxygen-mediated oxidation of functionalized pyrrolinones is another method to synthesize  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. Indeed, in basic conditions and in the presence of atmospheric oxygen, 1,5-dihydro-2H-pyrrol-2-ones were easily converted into  $\gamma$ -hydroxy- $\gamma$ -butyrolactams (Scheme 53).<sup>100,101</sup>

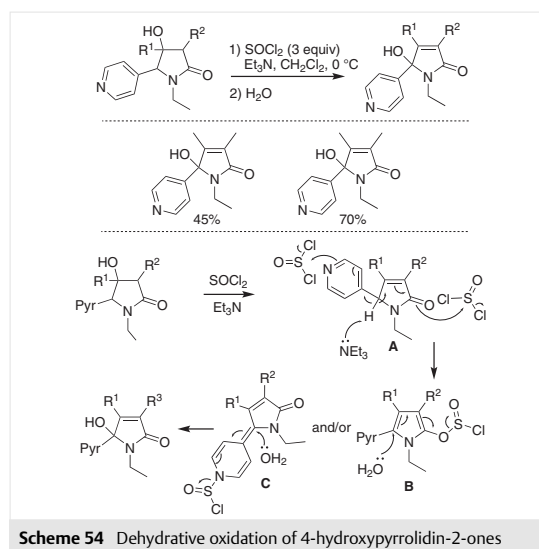


## 5 Miscellaneous

### 5.1 Dehydrative Oxidation of 4-Hydroxypyrrolidin-2-ones

Pigge and co-workers treated 4-hydroxypyrrolidin-2-ones with excess thionyl chloride in the presence of a base to generate  $\gamma$ -hydroxy- $\gamma$ -butyrolactams.<sup>102</sup> Indeed, by taking advantage of the dehydration properties of  $\text{SOCl}_2$ , the reaction first produces 1,5-dihydro-2H-pyrrol-2-one intermediate **A**. A further reaction of **A** with  $\text{SOCl}_2$  in the pres-

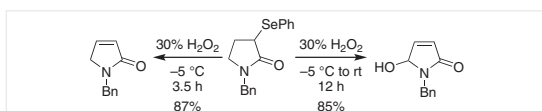
ence of base affords species **B** and/or **C**, which then undergoes a nucleophilic addition reaction with  $\text{H}_2\text{O}$  to form the  $\gamma$ -hydroxy- $\gamma$ -butyrolactam (Scheme 54).



### 5.2 Hydrogen Peroxide Oxidation

During the course of the selenoxide elimination reaction to prepare 1,5-dihydro-2H-pyrrol-2-one, Smith and Mun found that when the reaction was stirred for a longer time

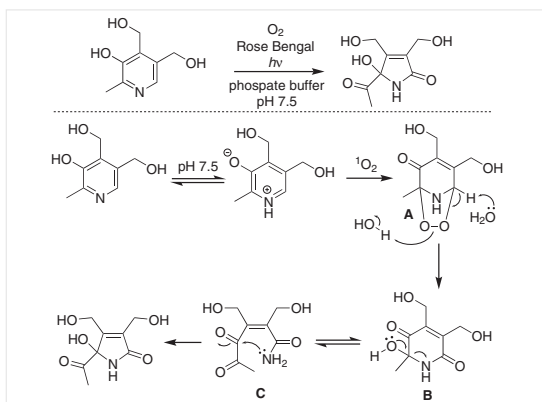
(12 h instead of 3.5 h), 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one was observed instead of the expected product (Scheme 55).<sup>103</sup>



**Scheme 55** Hydrogen peroxide oxidation

### 5.3 Singlet Oxygen Addition to Pyridoxines

In 2012, Hilmey and co-workers<sup>104</sup> reported an unexpected and unprecedented ring contraction of pyridoxines by a [3+2]-cycloaddition reaction in aqueous solution (phosphate buffer pH 7.5) to give  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. Under neutral pH conditions, pyridoxine exists as the zwitterion form which undergoes [3+2]-cycloaddition reaction with  $^1O_2$  to produce the corresponding endoperoxide **A**. Further proton elimination/peroxide cleavage/carbonyl formation gives the six-membered heterocycles **B** which contracts to the five-membered heterocycle via the open form intermediate **C** (Scheme 56). It is worth noting that photooxygenation ring contraction was also observed starting from diazepine and oxazepine.<sup>105</sup>



**Scheme 56** Ring contraction of pyridoxines

## 6 Conclusion

In summary, a plethora of methods have been highlighted in this review for the synthesis of  $\gamma$ -hydroxy- $\gamma$ -butyrolactams. These scaffolds, which are of great interest due to their presence in designed pharmaceutical molecules and numerous natural products displaying a broad spectrum of biological activities, are also relevant and versatile building blocks in organic synthesis. In this context, strategies for the construction of these  $\gamma$ -hydroxy- $\gamma$ -butyrolactams have triggered considerable attention and are still relevant today.

## Acknowledgment

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