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Transition-Metal Free Deconstructive Lactamization of Piperidines

Julio Romero-Ibañez, Silvano Cruz-Gregorio, Jacinto Sandoval-Lira, Julio M. Hernández-Pérez, Leticia Quintero, and Fernando Sartillo-Piscil*

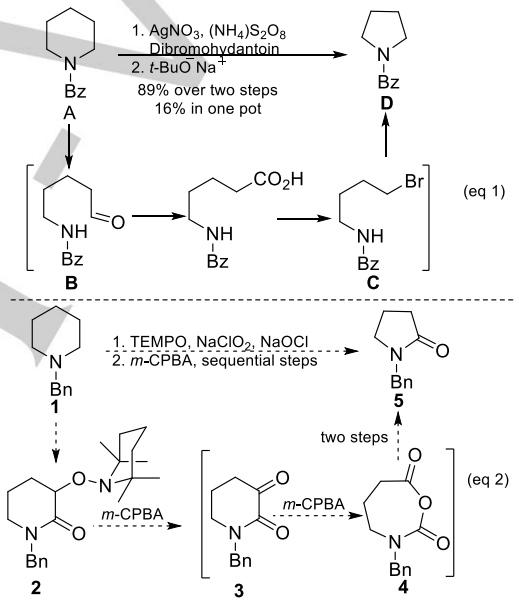
Dedication ((optional))

Abstract: One of the major synthetic challenges in organic synthesis is the activation or deconstructive functionalization of unreactive C(sp^3)−C(sp^3) bonds. This requires using transition or precious metal catalysts. However, we present here a deconstructive lactamization of piperidines without using transition metal catalysts. To this end, we use 3-alkoxyamino-2-piperidones, which were prepared from piperidines through a dual C(sp^3)−H oxidation, as transitory substrates. Experimental and theoretical studies confirm that this unprecedent lactamization occurs in a tandem manner involving an oxidative deamination of 3-alkoxyamino-2-piperidones to 3-keto-2-piperidones, followed by a regioselective Baeyer-Villiger oxidation to *N*-carboxyanhydride intermediates, which finally undergo a spontaneous and concerted decarboxylative intramolecular translactamization.

Transition metal catalysts have played a major role on the exponential advance of the "state-of-the-art" of organic synthesis.[1] Transition-metal catalyzed C−C bond coupling reactions,[2] Csp^3−H bond activation-functionalization of saturated compounds,[3] and Csp^3−Csp^3 bond cleavage-functionalization[4] are representative chemical transformations that have revolutionized the industrial and academic research. However, the economic and ecological cost of employing these reactive catalysts is high and is attracting the attention of chemists who believe that organic synthesis should be performed, not only with high efficiency and yields, but also with an economic and ecological approach.[5] Fortunately, a considerable number of remarkable transition-metal-free synthetic protocols are reported daily.[6-10]

In recent years, our research group has developed efficient, accessible, economic and environmentally friendly protocols for the functionalization of simple *N*-heterocycle substrates into relevant bioactive precursors.[11] The success of this new form of direct functionalization of pre-existing *N*-heterocycles lies on the highly selective C−H oxidation at the alpha position mediated by cheap and environmentally friendly reagents such as $NaClO_2$, NaOCl and TEMPO, in which, under modulated conditions, the C−H oxidation at the beta position can be achieved, even under catalytic conditions.[11a]

In this work, we are pleased to introduce a simple protocol that permits the transformation of piperidines to 2-pyrrolidinones via a deconstructive functionalization of a piperidine´s C(sp^3)−C(sp^3) single bond to pyrrolidinone´s C(sp^2)−N "single" bond. This can be attained either by a two-step or one pot protocol, but under transition-metal free conditions and using only cheap and environmentally-friendly reagents. We designed the title chemical transformation inspired by the seminal work of the Sarpong group,[12] in which they developed a silver-mediated deconstructive functionalization of piperidines into pyrrolidines in two sequential steps, and one pot protocol (Scheme 1)



Scheme 1. Silver-mediated deconstructive dehomologation of piperidines developed by Sarpong (eq 1),[12] and the transition-metal free deconstructive lactamization of piperidines proposed here (eq 2).

In Sarpong´s work, the C−H oxidation of a deactivated piperidine **A** allowed the initial C−N bond cleavage to amino aldehyde **B**, which after oxidation and decarboxylative halogenation provided the respective deconstructive halogenation product **C**. Finally, after treatment **C** with a base, the dehomolgated pyrrolidine **D** was obtained (eq 1, Scheme 1). In our approach, on the other hand, deconstructive functionalization of the sp^3 C−C bond at the alpha and beta positions of the respective piperidine was envisioned by applying the selective and dual C−H oxidation of tertiary piperidines **1** to 3-alkoxyaminolactams **2** mediated by $NaClO_2$, NaOCl and TEMPO.[11b,11c] Thereafter, precursor **2** would be transformed into keto lactam **3** via an oxidative deamination mediated by a suitable oxidizing reagent that would catalyze a regioselective Baeyer-Villiger (SBV)[13] oxidation to *N*-carboxyanhydride intermediate **4**. Finally, the respective 2-pyrrolidinone **5** would be obtained after a hydrolysis and an intramolecular amidation (eq 2, Scheme 1). The two major challenges of this synthesis

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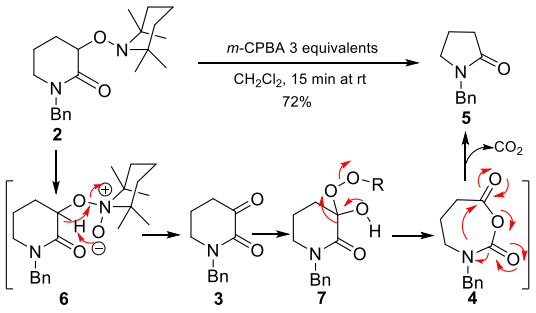
Supporting information for experimental and spectroscopic data for all products. Also theoretical details.((Please delete this text if not appropriate))

proposal would be the regioselective Baeyer-Villiger oxidation,[14] as well as the development of an efficient "one-pot" or sequential transformation of *N*-carboxyanhydride into the desired pyrrolidinones.

Following the plan depicted in Scheme 1 (eq 2), piperidine **1** was transformed into piperidone **2** with $NaClO_2$, NaOCl and TEMPO, and after adding 3 equivalents of *m*-CPBA to a solution of **2** in CH_2Cl_2, lactam **5** was unexpectedly obtained in 72% yield in 15 min. Remarkably, not only the BV reaction was highly selective, but also all the subsequent transformations, which were planned to occur in four separated steps, occurred in an unprecedent tandem fashion (Scheme 2). We postulate that this novel domino reaction begins with an oxidative deamination of **2** with *m*-CPBA to ketoamide **3** (via *N*-oxide intermediate **6**), followed by a regioselective BV reaction[13] of **3** to **4** (through a Criegee intermediate **7**), and finally, a concerted decarboxylative intramolecular translactamization of *N*-carboxyanhydride **4** (Scheme 2).

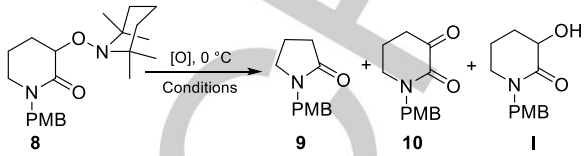


Scheme 2. Tandem translactamization of alkoxyamino lactam **2** to lactam **5**, and proposed intermediates.

Screening optimal reaction conditions were conducted with 3-alkoxyamino piperidone **8** (Table 1). Compound **8** was treated under the same reactions conditions as for **2**, and the expected 2-pyrrolidinone **9** was obtained with practically the same chemical yield (entry 1). Switching the solvent from CH_2Cl_2 to Et_2O improved the chemical yield to 88% (entry 2). Reducing the equivalents of *m*-CPBA, from 3.0 to 2.5, affected the chemical yield (entry 3). Poor yield of **9** was obtained when 1.5 equivalents were employed (entry 4). While lactam **8** was unreactive with H_2O_2 (entry 5) and Oxone (entry 6),[15] a moderate yield of lactam **9** was obtained when both oxidizing reagents were used as a mixture (entry 7). Further combinations of these oxidizing reagents produced worse yields. Because of an interrupted oxidative deamination, traces of hydroxylactam **I** were obtained in some cases (entries 1, 2, 4).

With the optimized reaction conditions for translactamization of 3-alkoxyamino lactams in hand, we proceed to establish the scope of the transition-metal free deconstructive lactamization (TMFDL) of piperidines, including, as a first step, the dual and tandem oxidation of piperidines to 3-alkoxyamine pyrrolidinones (Table 2). High chemical yields were obtained for the lactamization of piperidines **1** and **11** to lactams **5** and **9**, respectively. We thought that *m*-CPBA could be compatible with the oxidizing reagents employed for the dual oxidation, then a "one-pot" protocol was applied to piperidines **1** and **11** providing acceptable yields of lactams **5** and **9**. The regioselectivity in the Baeyer-Villiger reaction was tested with piperidines substituted at the C-4 position (**12**, **14**, **16**, **18**, **20**, **22**, **24**, and **28**, Table 2).

Table 1. Screening conditions for the direct translactamization 3-alkoxyamine lactam **8** to lactam **9**.[a]



Entry	[O]	Solvent	Time	Isolated yield[b]
1	*m*-CPBA (3)	CH_2Cl_2	10 min	**9** (71%)[c]
2	*m*-CPBA (3)	Et_2O	10 min	**9** (88%)[c]
3	*m*-CPBA (2.5)	Et_2O	10 min	**9** (45%)
4	*m*-CPBA (1.5)	Et_2O	20 min	**9** (12%) + **10** (13%)
5	H_2O_2 (15)	Et_2O	2 h	dnr[d]
6	Oxone (3)	Et_2O	2 h	dnr[d]
7	H_2O_2/Oxone (15/3)	CH_2Cl_2	12 h	**9** (67%)[c]

[a] Reactions performed at 0.03 mmol of 3-alkoxyamine piperidone. [b] Yields are reported after chromatography. [c] Traces of hydroxylactam **I** were detected. [d] dnr = did not react.

Good yields of pyrrolidinones were obtained not only for piperidines bearing 4-isobutyl (**13**, 56%), 4-ethyl (**15**, 65%), and 4-methyl (**17**, 63%) groups, but also for both 4-aryl substituted (**19**, 50%; and **21**, 51%). Both, ester and ether groups at the same position of the piperidine ring (**22** and **24**) gave acceptable yields of pyrrolidinones **23** and **25**, 46% and 42%, respectively. A similar result was obtained for the reaction from piperidine **26** to its respective pyrrolidinone **27** (42%). Unfortunately, albeit the dual C−H oxidation of 4-hydroxy-pirrolidine **28** proceeded in good yield (68%), translactamization of the respective 3-alkoxyamine piperidone (not shown in Table 2) did not occurred (Table 2).

The potential use of this novel synthetic methodology was demonstrated in the synthesis of (*S*)-4-hydroxy-2-pyrrolidinone (*S*)-**30**,[16] which is a key precursor of various bioactive products such as the oral antibiotic **CS-834**[17] and a nootropic agent oxiracetam (**31**).[18] In addition, the formal synthesis of (+)-harmicine (**32**)[19] was achieved by a simple application of TMFDL to indole piperidine **33** (Scheme 3). Proline derivative **34** was transformed into (*R*)-3-hydroxy-piperidine **35** in two sequential steps: first, a reduction of the ester group with $LiAlH_4$; and second, a ring expansion mediated by trifluoroacetic anhydride and quenched with NaOH.[20] As observed from the

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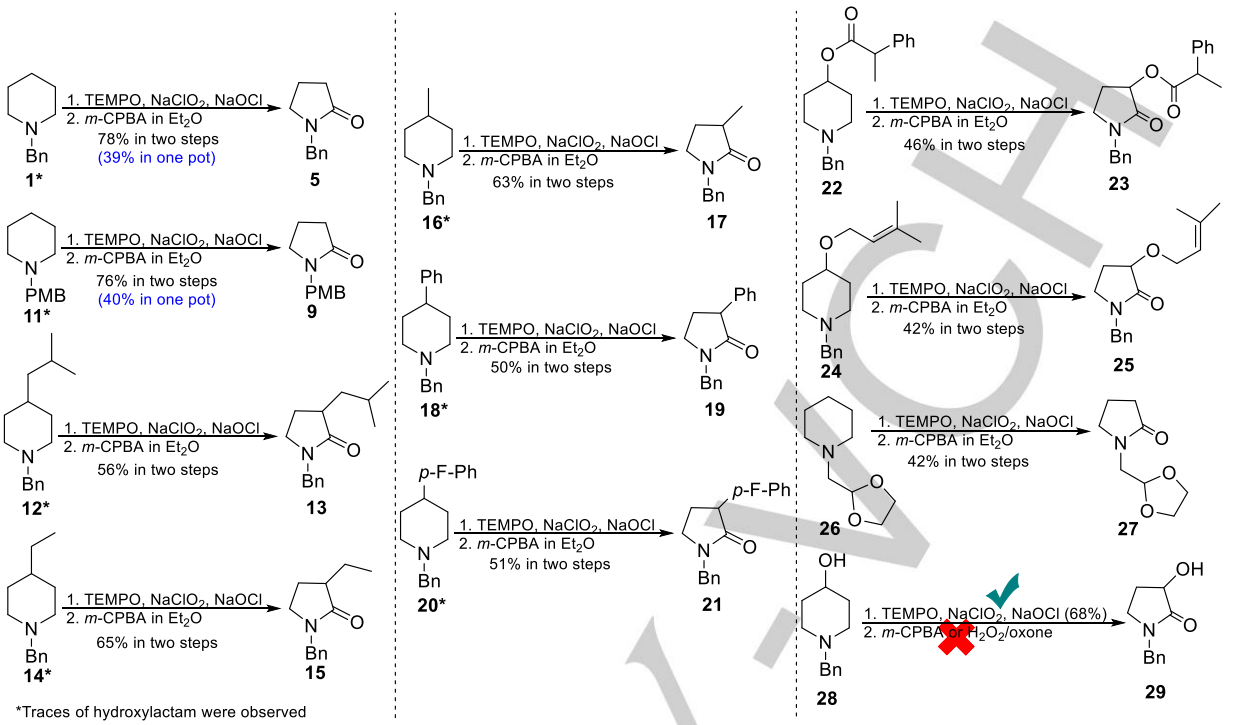
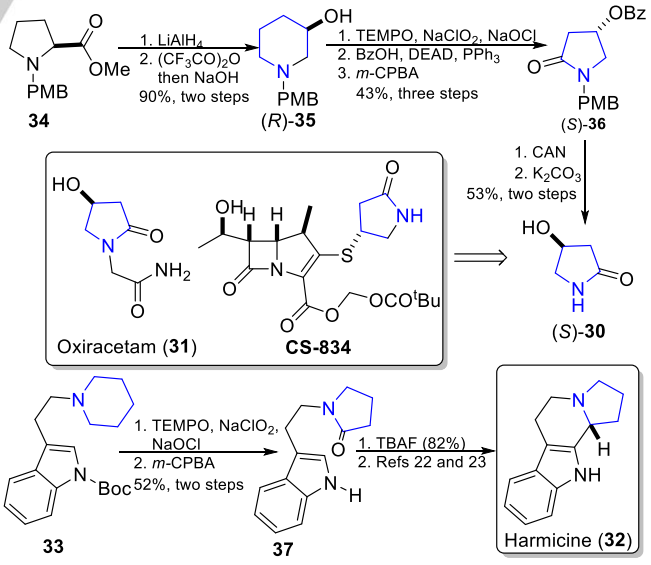
Table 2. Developing transition-metal free deconstructive lactamization (TMFDL) of piperidines.

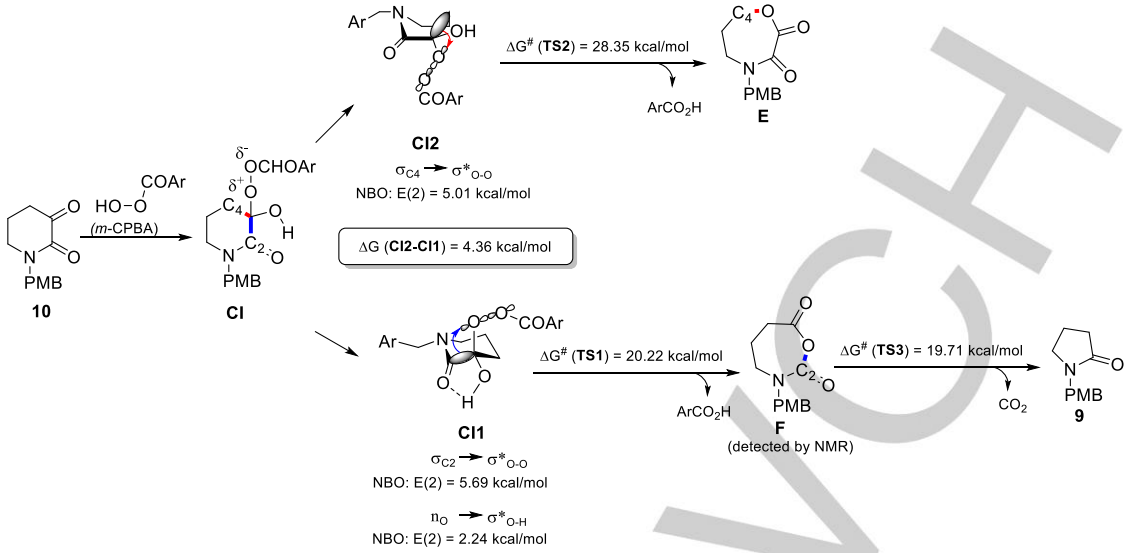


above, the regioselective BV reaction did not occur in the presence of a free hydroxyl group; thus, we decided to employ the Mitsunobu reaction[21] after the dual oxidation. This allowed to attain, not only the desired stereochemistry (3*S*), but also the protection of the hydroxyl group. Thus, chiral pirrolidinone (*S*)-**36** was prepared from (*R*)-**35** in three sequential steps. Removal of the protecting groups of (*S*)-**36** provided the target product (*S*)-**30** (Scheme 3). On the other hand, the indole derivative **33** was subjected to TMDFL, and pyrrolidinone **37** was obtained with a moderate yield. After removal of the Boc protecting group with TBAF, and following reported procedures,[22,23] the (+)-harmicine **32** can be obtained (Scheme 3).

In order to prove the formation of the putative *N*-carboxyanhydride intermediate and its concerted conversion to the lactam product, the reaction of keto lactam **10**[11b] with *m*-CPBA was conducted into the NMR tube. The NMR tube was charged with equimolar amounts of *m*-CPBA and **10** in $CDCl_3$. The *N*-carboxyanhydride **F**, lactam **9**, and the remaining starting material **10** with a 8:7:5 ratio, respectively, were observed after 3 min of stirring at 20 °C. The ratio in favor to product **9** changed to 1:8:2 in 20 min (see SI). The complete conversion of **10** to **9** was rapidly achieved by adding 0.5 equivalents of *m*-CPBA. Since intermediate **F** cannot be isolated, its molecular structure was confirmed by computational modeling of the ^{1}H NMR at B3LYP/6-31++G(2d,p)//B3LYP/6-31G(d) level of theory with the SMD model to describe the solvent effect [$CDCl_3$ (ε = 4.7)].[24] According to the prevailing mechanism of the BV, the Criegee intermediate (**CI**) favors the group migration of those who can stabilize better the partial positive charge.[25] Therefore, the migratory atom should be the C-4 atom, and not the C-2 atom from the carbonyl group (Scheme 4). Computational analysis at ωB97XD/6-311+G(d,p) level of theory[26] revealed the existence of two stable Criegee intermediate conformers (**CI1** and **CI2**) prone to form *N*-carboxyanhydride intermediates. Because of the presence of an intramolecular hydrogen bond (with an energy E(2) = 2.24 kcal/mol), Criegee intermediate **CI1** (in which C2−C3 bond and O−O bond are anti-periplanar oriented), is 4.36 kcal/mol more stable than **CI2**. From the optimization and the characterization of the **TS1** and **TS2** transition state structures



Scheme 3. Synthetic applications of the transition-metal free deconstructive lactamization (TMFDL) of piperidines.



Scheme 4. Regioselective BV and decarboxylative translactamization mechanism.

for **CI1** to **F** and for **CI2** to **E** reactions, respectively, we found that the former transformation occurs at much lower energetic cost ($\Delta G^{\#}$(**TS1**) = 20.22 kcal/mol) than the later ($\Delta G^{\#}$(**TS2**) = 28.35 kcal/mol). Additionally, the transformation of intermediate **F**, which was detected by ^{1}H NMR, into lactam **9**, was also computed. It was found that the activation energy for **F** to **9** is lower ($\Delta G^{\#}$(**TS3**) = 19.71 kcal/mol) than the activation energy for **CI1** to **F** reaction (20.22 kcal/mol), confirming that it also occurs in a concerted process (Scheme 4).

We have developed, under transition-metal free conditions and using environmentally friendly reagents, a new synthetic protocol that permits the access to 2-pyrrolidinones from simple tertiary piperidines via a selective oxidative ring contraction of N-substituted piperidines, either in two step or “one pot” protocol. The synthesis scope, synthetic applications and mechanistic findings of this novel synthetic technology offers, not only a promising alternative for development of a wide-range of bioactive pyrrolidinones and derivative molecules, but also a new synthetic disconnection complementary to the classical lactamization protocols.

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Keywords: Baeyer-Villiger • Decarboxylative translactamization • Deconstructive functionalization • Piperidines • Pyrrolidinones • Transition-metal free synthesis.

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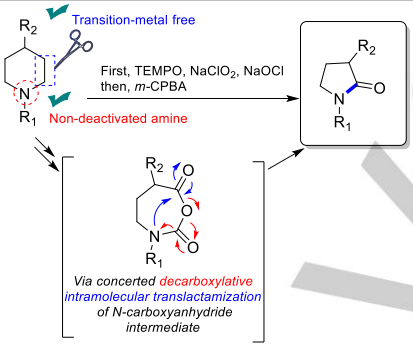
Transition-Metal Free Deconstructive Lactamization of Piperidines:

An unprecedent transition-metal free "one-pot" or two step protocol for the lactamization of piperidines is reported. This represent a new synthetic disconnection complementary to the classical lactamization protocols.



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