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Synthesis of Colibactin Pyrrolidono[3,4-*d*]pyridones via Regioselective C(sp^3)−H Activation

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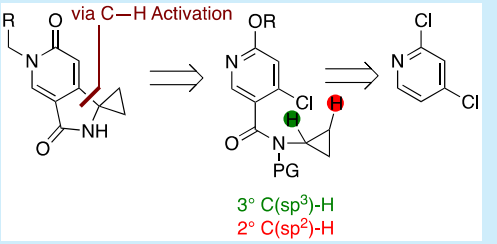
ABSTRACT: The synthesis of pyrrolidono[3,4-*d*]pyridones of relevance to putative genotoxic colibactin structures featuring a doubly conjugated 1,6-Michael acceptor system is reported. We investigated and implemented a highly selective Pd-catalyzed C(sp^3)−H activation reaction as a key step and further functionalized the pyridone core. Evaluating the role of this structural unit of relevance to colibactin, we found that this structure displayed a high degree of stability toward both acidic conditions and nucleophiles.



The term "human microbiota" refers to a wide range of different microorganisms such as bacteria, fungi, and viruses residing in and on the human body that have been implied as humans' second genome.[1] Little is known about their interkingdom interaction and their effect on human health or disease progression.[2] Recently, the bacteria *Helicobacter pylori* and *Klebsiella oxytoca* have been identified to induce colitis, albeit by different mechanisms.[3] Over a decade ago, the Oswald group reported that certain commensal and extra-intestinal *Escherichia coli* strains of the phylogenetic group B2 can cause megalocytosis and cell cycle arrest.[4] These scientists identified and linked cytotoxicity to a 54 kilobase *pks* genomic island harboring a hybrid non-ribosomal peptide synthetase−polyketide synthase (NRPS-PKS) and provided evidence for the whole gene cluster linked to its cytotoxicity.[4]

Over the last 15 years, the isolation and characterization of the small-molecule compounds resulting from this cluster (the so-called (pre)-colibactins) proved to be challenging, presumably because of their instability, difficulties in heterologous expression, and fermentation (Figure 1).[5] A number of metabolites have been isolated, such as pyridone **1**, monothiazole-substituted **2**, bisthiazole-substituted **3**, and complex macrocycle **4**.[5] Furthermore, lactam **5** was proposed to bear the colibactin warhead,[5a] and the recently proposed active genotoxic metabolite **6**[5g,h] has been characterized and linked to the *pks* island and/or its mutants. Seminal synthetic and reactivity studies by Herzon, Crawford, and their coworkers led them to conclude that compounds similar to lactam **6**, albeit monomeric, and not pyridones such as **1**−**3**, alkylate DNA, with the pyridones being stable.[5j] All of these structures feature a cyclopropyl ring (Figure 1, highlighted) in conjugation with 1,4- or 1,6-Michael acceptors, thereby likely increasing their electrophilic character. Another feature of these compounds includes a prodrug mechanism, where a *clb*-encoded peptidase cleaves the *N*-myristoyl-D-asparagine moiety to generate compounds with higher activity and

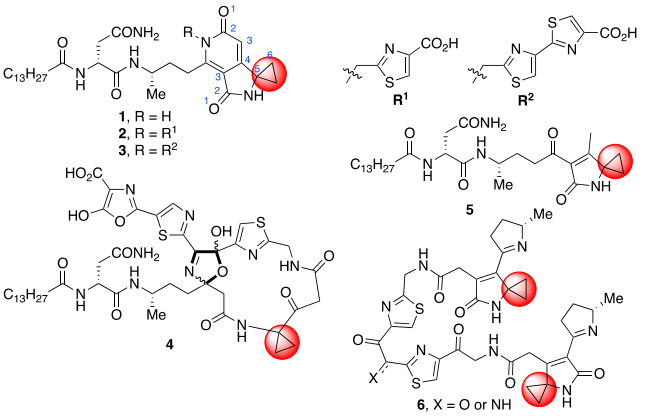


Figure 1. Natural compounds isolated from the clb *E. coli* strain of putative relevance to the (pre)-colibactin structure of the *pks* islands.

reactivity.[6,7] In the context of recent studies of pyridones as neuritogenic compounds by us and others[8] and the prevalence of pyridone-containing natural products and pharmacophores,[9] we directed our attention to pyrrolidono[3,4-*d*]pyridones **1**−**3**, as these complex heterocyclic compounds have incorporated the cyclopropyl ring in a unique double 1,6-relationship through conjugation, rendering them structurally interesting Michael acceptors. In addition, Michael acceptors and other covalent modifiers have gained strong interest in drug discovery efforts over the last years.[10] In addition to these

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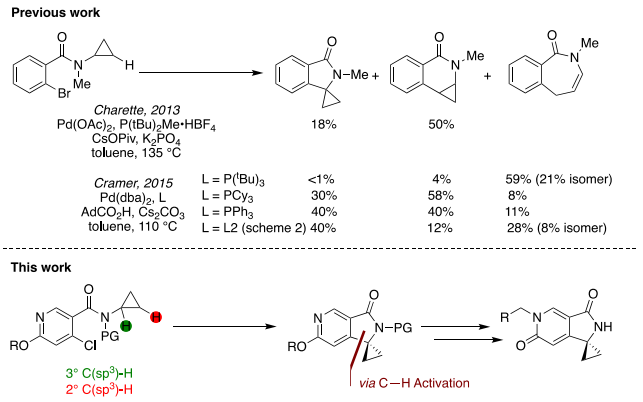
biological questions and structural requirements for addition, we were also interested in identifying a novel route toward these compounds, which should facilitate access to the target structure and derivatives for chemical and biological evaluation. Therefore, we report on a novel access to this class of compounds via a regioselective, Pd-catalyzed C(sp^3)–H activation approach.[11]

The development and application of powerful C–H activation methodologies has gained tremendous interest and been successfully implemented in many synthetic endeavors.[12] Promising literature precedents for C–H functionalization of cyclopropyl amides (Scheme 1) led us to examine this

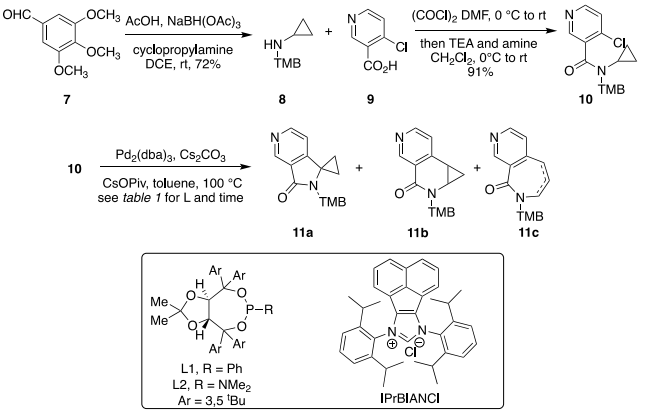
Scheme 1. C–H Functionalization of Cyclopropyl Amides via Pd Catalysis



synthetic approach. Fagnou and coauthors demonstrated the superiority of soluble organic additives like pivaloic acid for C–H activation protocols, and his group established a C–H functionalization of cyclopropyl carbamates leading to quinolines after oxidation.[13] The group of Charette observed in 2013 that cyclopropyl benzamides are less prone to ring opening in the presence of external bases.[14] Cramer and co-workers investigated the effect of ligands, and a 1:1 ratio between methine and methylene C–H bond cleavage was obtained with triphenylphosphine as the ligand and 1-adamantanecarboxylate as the base.[15] In all previous literature studies, the desired five-membered-ring compounds were never obtained as major products. From all of these observations, the following challenges had to be overcome in the context of this study: (1) the different electronic nature of pyridine amides compared with benzene derivatives; (2) use of chloro precursors instead of more reactive bromo precursors, (3) successfully addressing the regioselectivity bias to favor methine over methylene C–H activation; and (4) suppressing the inherent susceptibility of the cyclopropyl group for ring opening. The chloro substituent was preferred over the more reactive bromo or iodo substituents, as we sought to first introduce amide or carboxylate groups by cross-coupling or halogen–metal exchange on the C–Br bond before the C–H activation step (vide infra).

The challenges listed above were first investigated in the context of a model substrate that was synthesized in two steps (Scheme 2). Reductive amination of 3,4,5-trimethoxybenzaldehyde (**7**) with cyclopropylamine using sodium triacetoxyborohydride gave secondary amine **8** in 72% yield.[16] 4-Chloronicotinic acid (**9**) was converted in situ to the corresponding acyl chloride ($(COCl)_2$, catalytic DMF), and subsequent addition of **8** in the presence of triethylamine

Scheme 2. Investigation of the C–H Activation Reaction on a Model Substrate (TMB = 3,4,5-Trimethoxybenzyl)



furnished amide **10** in 91% yield.[17] With intermediate **10** in hand, the stage for the C–H functionalization was set, and the results are summarized in Table 1. Literature reports suggest

Table 1. Conditions for the Key C–H Activation Reaction on a Model Substrate

entry	ligand	time (h)	**11a**:**11b**:**11c**[a] (isolated yield)
1	PCy_3·HBF_4	21	1:5.5:0 (83%)
2	IPrCl	16	1:2:0
3	$SIPrBF_4$	16	1.2:1:0 (86%)
4[b]	$IAdBF_4$	17	2.2:0:1 (45%)
5	IPrBIANCl	16	1:2.8:n.d.
6	L1	22	n.d.
7	L2	22	n.d.

[a]The ratios were determined by analysis of the reaction mixtures by ^{1}H NMR spectroscopy. [b]105 °C for 1 h and 110 °C for 15 h.

that the ligand has the strongest influence on the outcome of the reaction, while other parameters such as the Pd source, base, additive, and solvent were based on recent findings.[14,15] The following parameters were set: Pd_2dba_3, Cs_2CO_3, CsOPiv as a soluble organic base, toluene as the solvent, and generally a temperature of 100 °C, since it was sufficient for the reactivity. Electron-rich PCy_3·HBF_4 gave an inseparable mixture of **11a** and **11b** (1:5.5, 83% yield) in favor of the undesired six-membered ring (entry 1, Table 1), and no formation of the seven membered ring derivative **11c** was observed. Despite the strong C–Cl bond in precursor **10**, oxidative addition took place at 100 °C. The electron-withdrawing nitrogen atom activates the γ-position, thereby facilitating the oxidative addition. N-Heterocyclic carbene (NHC) ligands were investigated next: the ratio dropped to 1:2 when the ligand IPrCl was used, and when using the ligand $SIPrBF_4$ was used, the five-membered-ring compound **11a** dominated (1.2:1, 86% yield) without any ring opening observed (entries 2 and 3, Table 1). This increase prompted us to evaluate other NHC ligands, and the ligand $IAdBF_4$ was selective toward **11a** in 31% yield along with the ring-opened compound **11c** in 14% yield as separable compounds (entry 4, Table 1), albeit in the presence of other byproducts. The last ligand from the NHC series, IPrBIANCl, led to preferred formation of the six-membered-ring compound **11b** (entry 5, Table 1). The TADDOL-based phosphonite and phosphoramidite ligands did not yield products (entries 6 and 7, Table

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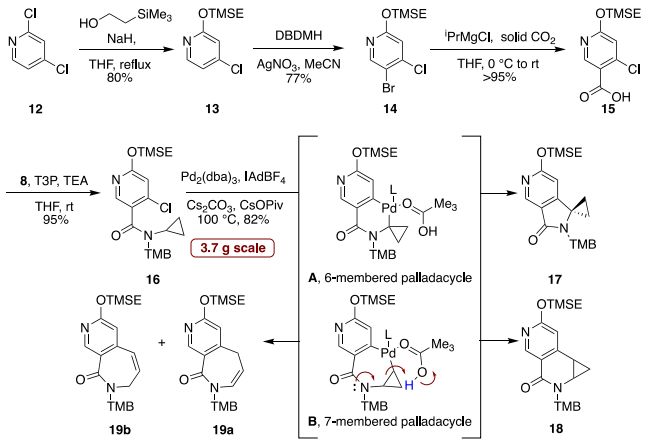
1), and in general NHC ligands proved superior in this screening, although no clear trends could be obtained with respect to their electronic and steric properties.

We then proceeded to the desired substrate with the insight gained from the C−H activation screening (Scheme 3). 2,4-

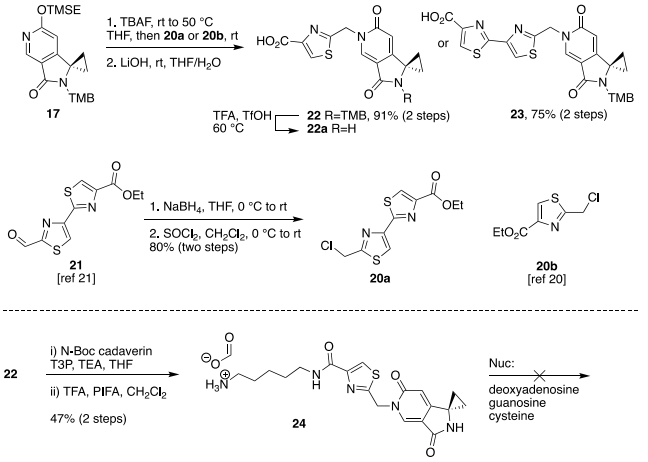
Scheme 3. Synthesis of Colibactin Pyrrolidono[3,4-*d*]pyridones via C−H Activation and Selective *N*-Alkylation (TMSE = Trimethylsilylethyl)



Dichloropyridine (**12**) was found to be a suitable starting material, and nucleophilic aromatic substitution with 2-(trimethylsilyl)ethanol provided the 2-substituted product **13** with high regioselectivity in 77% yield.[18] Selective *ortho* bromination was achieved with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and catalytic $AgNO_3$ to yield dihalogenated pyridine **14** (77%). Silver(I) was found to shorten the reaction time significantly. Mg halogen exchange following the procedure of Knochel[19] and subsequent quenching of the magnesiated species with solid carbon dioxide yielded acid **15** (>95%). Propylphosphonic anhydride (T3P)-mediated coupling of acid **15** and secondary amine **8** furnished amide **16** in 95% yield. The Arduengo carbene IAd was selected as the optimal ligand, as it provided higher selectivity toward the desired five-membered ring in this substrate (data not shown), resulting in easier purification. On the other side, the five-membered ring was the dominant product with the ligand SIPrCl, but other byproducts accompanied the transformation with this ligand. To this goal, cyclopropyl amide **16** was reacted with Pd_2dba_3, Cs_2CO_3, CsOPiv, and $IAdBF_4$ in toluene at a reaction temperature of 100 °C. The desired compound was formed exclusively according to analysis of the crude reaction mixture by ^1H NMR spectroscopy, and after purification bicyclic pyrrolidono[3,4-*d*]pyridine **17** was isolated in 82% yield. The interplay between the bulky, electron-rich ligand (IAd) and a bulky organic base (pivalate) facilitates the highly challenging C(sp^3)−H activation. In this case, the formation of the six-membered palladacycle makes the ring opening impossible (intermediate A, Scheme 3). On the other side, the seven-membered ring (intermediate B, Scheme 3) can either undergo reductive elimination to give **18** or ring opening to afford **19a** or its isomer **19b**. The Charette group observed these pathways to be ligand-dependent, which is supported by the results outlined herein.[14]

The mono- and bisthiazole electrophiles were synthesized next (Scheme 4), as they were found in **2** and **3**. The electrophile **20b** is known in the literature,[20] and **20a** was

Scheme 4. Functionalization of the Pyridone Core and Biological Evaluation



synthesized in two steps from known aldehyde **21** (three steps from the literature).[21] **21** was reduced with sodium borohydride to give the corresponding alcohol, which was converted to the chloride in the presence of thionyl chloride. This procedure gave the desired electrophile **20a** in 80% yield over two steps (Scheme 4).[20]

To access the pyridone core, a one-pot deprotection/alkylation protocol was developed (Scheme 4). Pyridine **17** was treated with tetrabutylammonium fluoride in THF at 50 °C to remove the 2-(trimethylsilyl)ethyl protecting group, and after the reaction mixture cooled to rt, electrophiles **20a** and **20b** were directly added to the mixture. Single compounds were isolated for both cases, and the thermodynamically more stable *N*-alkylation was determined through 2D NMR spectroscopy (HSQC, HMBC).[22] Saponification with lithium hydroxide in THF/water mixtures yielded the free acids **22** (91% yield over two steps) and **23** (75% yield over two steps). Removal of the 3,4,5-trimethoxybenzyl protecting group was targeted next. Acid **22** showed no deprotection or decomposition in trifluoroacetic acid as the solvent, but addition of trifluoromethanesulfonic acid (25 equiv) showed full deprotection to give **22a** as monitored by UHPLC-MS. This observation highlights the stability of **22**, in particular the cyclopropyl group, toward acidic conditions. We further functionalized acid **22** with *N*-Boc-cadaverine under T3P-mediated coupling, followed by removal of the Boc and 3,4,5-trimethoxybenzyl groups using a combination of TFA and [bis(trifluoroacetoxy)iodo]benzene (PIFA) to yield **24** (47% yield over two steps). The addition of PIFA as the oxidant was crucial for smooth 3,4,5-TMB deprotection.[23] The additional amino functionality in **24** renders the compound more water-soluble. Surprisingly, the target cyclopropyl pyridone **24** resisted nucleophilic attack by deoxyadenosine, guanosine, and cysteine in water as monitored by UHPLC-MS. If these systems are sufficiently conjugated, ring opening of the cyclopropyl group by different nucleophiles like amines or water can occur,[24] but **24** shows an unusually high stability under the evaluated conditions and does not fit into the common experimental observations of related electrophiles.

In summary, we have presented a short and straightforward synthetic route to pyridones containing 1,6-Michael acceptors that are structurally related to precolibactin metabolites. En route, we developed a highly regioselective tertiary C−H functionalization of the cyclopropyl ring, contributing to its

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activation mode. Furthermore, a one-step protocol with selective *N*-alkylation after protecting group removal furnished the desired Michael acceptor. Future studies might shed light on the biological activity and chemical reactivity of these compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02385.

Experimental procedures, characterization data, and copies of ^{1}H, ^{13}C, and 2D NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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