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Divergent Access to (1,1) and (1,2)-Azidolactones from Alkenes using Hypervalent Iodine Reagents

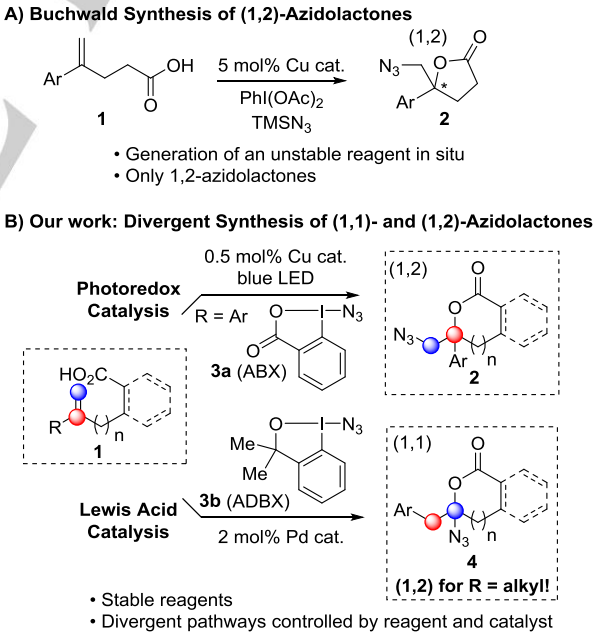
Sébastien Alazet, Franck Le Vaillant, Stefano Nicolai, Thibaut Courant and Jerome Waser[*]

Dedication

Abstract: *A versatile synthesis of azidolactones through azidation and cyclization of carboxylic acids onto alkenes has been developed. Based on either photoredox or palladium catalysis, (1,1) and (1,2) azido lactones can be selectively synthesized. The choice of catalyst and benziodoxol(on)e reagent serving as azide source was essential to initiate either a radical or Lewis Acid mediated process with divergent outcome. These transformations were carried out under mild conditions using a low catalyst loading and gave access to a large scope of azido lactones.*

Amino lactones have found widespread applications in natural product synthesis and in medicinal chemistry.[1] Furthermore, they serve as versatile starting materials for accessing other important building blocks, such as amino alcohols.[2] As non-basic precursors of amines, azides are highly useful synthetic intermediates on the way to nitrogen-rich compounds. They can also be transformed easily into various other nitrogen-containing functional groups.[3] Therefore, azidolactones are versatile and convenient precursors of both amino lactones and alcohols. Nevertheless, the preparation of azidolactones is usually based on multi-step protocols and lacks efficiency. The installation of the azido group commonly proceeds through substitution reactions on pre-functionalized substrates, such as halides.[4] Very recently, a copper catalyzed enantioselective radical azidocarboxylation of alkenes was developed by Buchwald and co-workers using phenyliodine diacetate (PIDA) and $TMSN_3$ as azide source, giving access to (1,2)-azidolactones **2** (Scheme 1, **A**).[5] However, this method is based on the in situ formation of highly reactive and potentially explosive hypervalent iodine reagents for the generation of the needed azide radical. Furthermore, this approach is limited to the synthesis of (1,2)-azidolactones: access to the (1,1) regioisomers, if possible from the same starting materials, would be highly attractive to extend the range of accessible azidolactones. (1,1)-Azidolactones are a largely unexplored class of compounds, which have been reported only rarely in the literature.[6]

In recent years, benziodoxol(on)es, a class of stable cyclic hypervalent iodine reagents, have emerged as privileged reagents for the transfer of functional groups via non-conventional reactivity.[7] AzidoBenziodoXolone (ABX, **3a**) and AzidoDimethyl-BenziodoXole (ADBX, **3b)** (Scheme 1) have been first described by Zhdankin and co-workers[8] and are stable solids decomposing at temperature higher than 100 °C.[9] They have been used as azide transfer reagents in presence of metal catalysts, relying either on radical-based[8,10] or Lewis-acid mediated pathways.[11] In particular, the azidation of styrene-type double bonds has recently attracted much interest and ABX (**3a**) and ADBX (**3b**) have emerged as good sources of azide radicals under reductive conditions.[10a,h,j,l] In 2015, Greaney and co-workers reported the photoredox-catalyzed nucleoazidation of styrenes using the Sauvage/McMillin catalyst $Cu(dap)_2Cl$[12] and ABX reagent **3a**, resulting in particularly mild reaction conditions.[10h] On the other hand, the azidation of ketoesters and silyl enol ethers has been successful in the presence of Lewis acids.[11] Nevertheless, to the best of our knowledge, azidobenziodoxol(on)es have never been used in the synthesis of azidolactones.



Scheme 1. Synthesis of Azidolactones from Alkenes.

Herein, we report the first synthesis of azidolactones based on the use of azidobenziodoxol(on)es (Scheme 1, **B**). The diverging behavior of ABX (**3a**) and ADBX (**3b**) in presence of metal catalysts led to either a radical-based or Lewis Acid mediated pathway, allowing the selective formation of (1,2)- or (1,1)-azidolactones **2** and **4** starting from styrene derivatives. The former was achieved under mild photoredox conditions using visible light irradiation and only 0.5 mol% $Cu(dap)_2Cl$ as catalyst,

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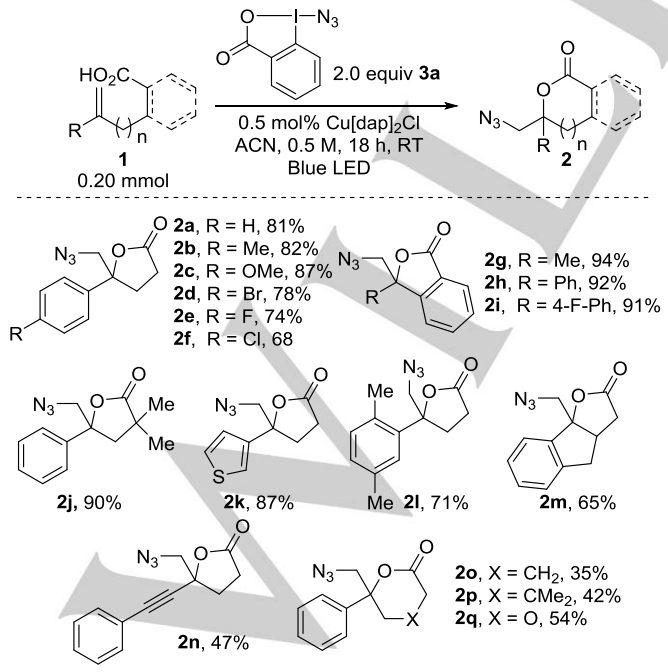
whereas the later was realized by Lewis acid activation of the hypervalent iodine reagent, involving an aryl migration step. Furthermore, the synthesis of (1,2)-azidolactones starting from olefins without arene substituent was possible using Lewis acid activation.

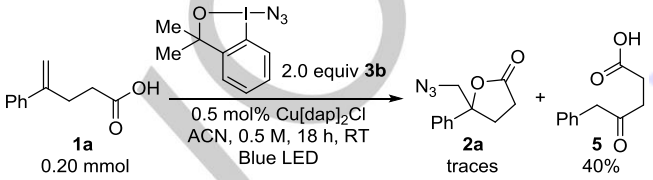
Based on the impressive work of Greaney and co-workers,[10h] we started our investigations with the photoredox catalysis strategy for the formation of (1,2)-azidolactone **2** from unsaturated carboxylic acid **1** (Scheme 2). Only ABX (**3a**) was successful in this transformation. Upon a fine adjustment of the reaction conditions,[13] the desired azidolactone **2a** could be isolated in 81% yield with 0.5 mol% of the photoredox catalyst under blue LED irradiation. Interestingly, while the reaction also worked in the absence of light, conversion to product **2a** dropped to 20%. This indicated that a radical chain process was possible, but less efficient. Using the combination of PIDA and $TMSN_3$ for azide radical formation,[5] only traces of **2a** were detected.

With this simple protocol for azidation in hands, we investigated the scope of the reaction (Scheme 2). A broad series of unsaturated carboxylic acids **1** containing substituted aryl groups was converted into the corresponding azidolactones **2** in good to excellent yields. Electron rich (**2b**, **2c**) as well as halogen-substituted arenes (**2d-f**) were well tolerated. A more rigid benzene backbone led to excellent yields of (1,2)-azido-phthalide derivatives **2g-i**. Dimethyl-substituted lactone **2j** was also obtained in 90% yield. A thiophene heterocycle was compatible with the reaction conditions (**2k**, 87%). An aromatic ring bearing a group in the *ortho* position was also tolerated (**2l**, 71%). Tricyclic (1,2)-azido-γ-butyrolactone **2m** was obtained in 65% yield. When enoic acid **1n** containing a 1,3-enyne motif was used, azidation product **2n** was formed in 47% yield. Importantly, (1,2)-azido-δ-lactones could be also obtained under the same reaction conditions, although lower yields were observed (product **2o-q**). Scale up of the reaction demonstrated that even lower catalyst loadings were possible: 1.0 g of **2e** was isolated in 82% yield using only 0.05 mol% catalyst.



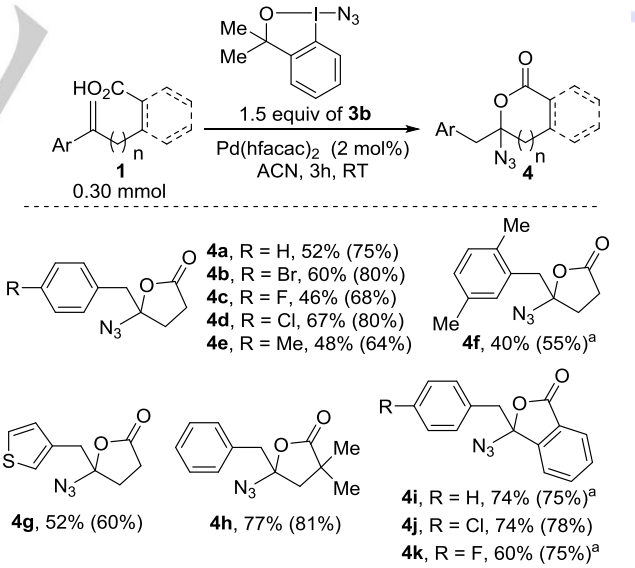
Scheme 2. Scope of the (1,2)-azidolactonization.

In contrast, when ADBX (**3b**) was used instead of ABX (**3a**) under the optimized photoredox conditions, only traces of (1,2)-azido-γ-butyrolactones **2a** were observed. The major product was 4-oxo-5-phenylpentanoic acid (**5**), which was isolated in 40% yield. (Equation 1) We speculated that **5** could originate from the hydrolysis of a (1,1)-azidolactone **4a** formed from reaction of the hypervalent iodine reagent with the double bond followed by 1,2-phenyl migration. In fact, such rearrangements have been observed for oxygenation or fluorination,[14] but are unprecedented for azidation with benziodoxole reagents. In this case, the copper catalyst probably acted as a Lewis acid to activate ADBX (**3b**) and not as a redox active catalyst able to generate the azide radical after a SET event.



Equation 1. Reaction of **1a** with ADBX (**3b**).

In fact, in presence of several Lewis acid catalysts such as $Zn(OTf)_2$, $In(OTf)_3$ and $Sn(OTf)_2$, (1,1)-azidolactone **4a** could be isolated as the major product.[13] $Pd(hfacac)_2$ (2 mol%) was identified as the best catalyst for this transformation leading to **4** in 75% yield by NMR. $Sn(OTf)_2$ provided similar results, but with lower reproducibility. The low catalyst loading is noteworthy, as most reported oxidative rearrangements required stoichiometric amounts of Lewis or Brønsted acids.[14] Although **4a** was sensitive to hydrolysis, it was still possible to purify it by column chromatography (52% pure **4a** isolated).



Scheme 3. Scope of (1,1)-azidolactonization of **1**. (isolated yield given, NMR yield in brackets). a) Isolated as a mixture with 2-(2-iodophenyl)propan-2-ol.

The reaction worked efficiently in the presence of halogen and methyl substituents on the aromatic ring, affording products **4b-f** in 55-80% yield. A thiophenyl group was also able to migrate, affording **4g** in 52% isolated yield. A geminal dimethyl substituted substrate **1h** gave the more stable azido lactone **4h** in 77% isolated

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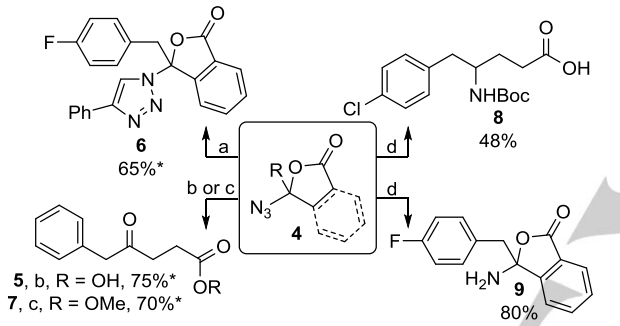
yield. Finally, (1,1)-azido-phthalide derivatives **4i**, **4j**, **4k** were also generated in high yields.

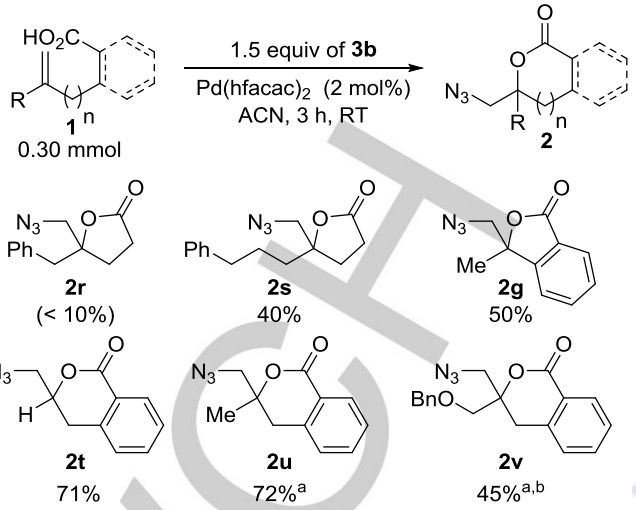
Due to the high sensitivity of the obtained (1,1)-azidolactones, the direct modification of the crude products was then investigated (Scheme 4). Copper catalyzed cycloaddition starting from **4k** and phenylacetylene gave triazole **6** as a stable crystalline solid in 65% yield over two steps starting from the olefin. Hydrogenation of the crude reaction mixture containing **4a** in EtOAc, using 5 mol% of Pd/C, afforded ketone **5** in 75% yield over two steps.[15] The γ-ketoester could be selectively generated through the hydrogenation of the crude material of **4a** in methanol in 70% yield over two steps. When using 10 mol% of Pt black as catalyst with (1,1)-azido-γ-butyrolactone **4d** in the presence of Boc_2O, the N-Boc protected Gamma AminoButyric Acid (GABA) derivative **8** was isolated in 48% yield. The GABA motif is commonly found in many bioactive compounds and is an important target in synthetic chemistry.[16] In the case of (1,1)-azido-phthalide derivative **4k**, only azide reduction was observed under Pt/C catalysis and the (1,1)-amino-phthalide **9** was isolated in 80% yield. These successful transformations demonstrated the potential of (1,1)-azidolactones as useful building blocks.



Scheme 4. Product modifications. *Isolated yields over two steps from **1**. Reaction conditions: a) CuI (10 mol%), Et_3N (3.0 equiv.), phenylacetylene (2.0 equiv.), THF, 25°C; b) H_2, Pd/C (5 mol%), EtOAc, 25 °C; c) H_2, Pd/C (2.5 mol%), MeOH, 25 °C; d) H_2, Pt black (10 mol%), Boc_2O (2.0 equiv.), THF, 25 °C.

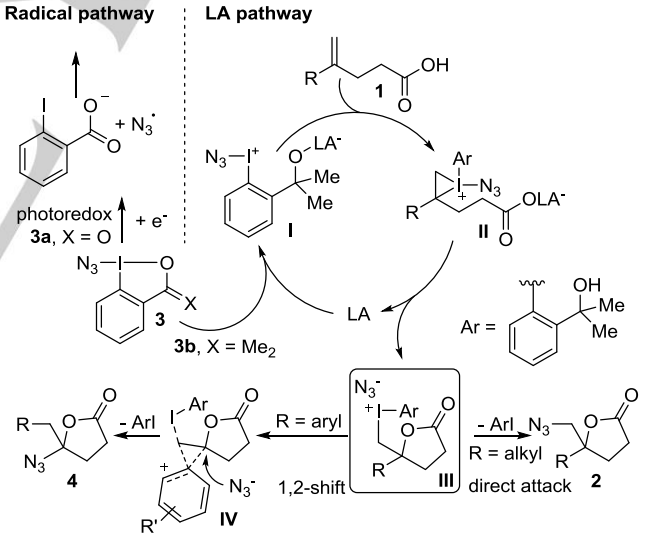
In order to investigate the generality of the 1,2-shift, we then replaced the aryl substituent by a simple alkyl group (Scheme 5). No (1,1)-azidolactone was obtained with a benzyl group: only traces of (1,2)-azidolactonization product **2r** could be observed. 1,2-Azidolactone **2s** could be obtained in 40% with a phenyl group in γ position to the alkene. Interestingly, compounds **2s** is not formed under photoredox conditions, as an aryl group on the alkene is required for oxidation of the carbon centered radical intermediate. Better yields were obtained with more rigid substrates derived from benzoic acid (products **2g** and **2t-v**). γ-lactone **2g** can be synthesized in better yield under photoredox conditions, but δ-lactone **2t-v** can be accessed only with Lewis acid catalysis, showing that the two methods are highly complementary.

Based on the precedence in literature on radical and Lewis acid pathways with hypervalent iodine reagents,[10,14] a speculative mechanism can be proposed for the developed transformations (Scheme 6). The better results obtained with ABX (**3a**) under photoredox conditions could be due to its expected stronger oxidant character when compared to ADBX (**3b**).[17] In contrast, the Lewis acid catalytic cycle would be initiated by the activation of ADBX (**1b**).[18] The resulting more electrophilic complex **I** will react with alkene **1** to give iodocyclopropylium cation **II**.



Scheme 5. Lewis acid catalyzed synthesis of (1,2)-azidolactones. a) 20 h of reaction. b) 10 mol% of $Pd(hfacac)_2$ were used.

A proton transfer can also be expected from the carboxylic acid to the more basic alkoxide, a key step to promote catalyst turnover only possible with **3b**. Ring opening through the attack of the carboxylic acid delivers then the highly electrophilic intermediate **III**. In case of aliphatic substituents, direct substitution with the azide would occur, leading to (1,2)-azidolactones **2**. In case of aryl substituents, 1,2-migration via a phenonium ion or a non-classical carbocation **IV** is faster and gives product **4a**. Further works will be needed to support this speculative mechanism.



Scheme 6. Speculative reaction mechanism.

In conclusion, we have reported a general and versatile synthesis of azidolactones starting from alkene-containing carboxylic acids. A large range of (1,1) and (1,2)-azidolactones were obtained selectively in high yields and with broad functional group tolerance. The fine modulation of the reactivity possible for benziodoxolone reagents was key to enable either a photoredox or a Lewis acid pathway to access (1,1)- and (1,2)-azidolactones respectively. These results further establish the exceptional potential of cyclic hypervalent iodine reagents for group transfer reactions and will allow a broader use of azidolactones as useful building blocks in synthetic and medicinal chemistry.

Acknowledgements

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Keywords: Azides, lactones, hypervalent iodine, photoredox, 1,2 shift.

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[15] In principle, a simple hydrolysis would also lead to the same compound. Nevertheless, better yields were obtained under hydrogenation conditions, probably because prior reduction of the azide facilitates hydrolysis under mild conditions.

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[18] At this stage, a redox catalytic cycle involving different oxidation states of palladium cannot be excluded, but it appears less probable as several Lewis acids were able to catalyze the reactions.

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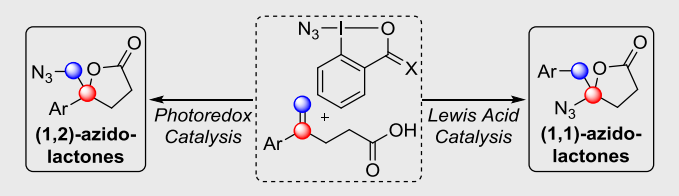

*Sébastien Alazet, Franck Le Vaillant, Stéfano Nicolai, Thibaut Courant and Jerome Waser**

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From one to both: *A versatile synthesis of azidolactones from alkenes and carboxylic acids has been developed based on photoredox and palladium catalysis. (1,1) and (1,2)-azido lactones can be selectively synthesized through the choice of benziodoxole reagent and catalyst. These transformations have been carried out under mild conditions using low catalyst loading and give access to a large scope of azidolactones.*