Cyclization

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Mild ArI-Catalyzed C(sp^2)–H or C(sp^3)–H Functionalization/C–O Formation: An Intriguing Catalyst-Controlled Selectivity Switch**

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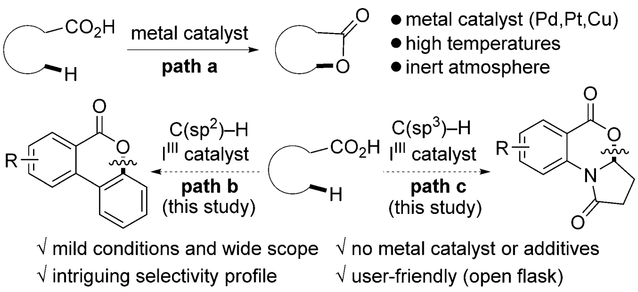
Abstract: *A tandem C(sp^2)–H and C(sp^3)–H functionalization/C–O bond formation catalyzed by iodine(III) reagents generated in situ has been developed. The method shows wide scope under mild conditions and exhibits an unprecedented selectivity profile that can be switched depending on the catalyst employed.*

Dramatic progress in the field of C–H functionalization has enabled the design of unconventional synthetic strategies.[1] Whereas a myriad of catalytic C–C and C–N bond-forming reactions have been developed, C–O bond formation has received much less attention,[2] partly owing to the large energy gap between M–O HOMO and M–C LUMO frontier orbitals.[3] Thus, the development of an innovative, yet practical, C–H functionalization/C–O bond-forming process has become a goal for synthetic chemists.[4,5] The preparation of benzolactones is an ideal target, since compounds such as the lamellarins and cytosporones, among others, show attractive biological properties.[6]

We[7] and others[8] have reported the synthesis of benzolactones through platinum- or palladium-catalyzed C–H functionalization/C–O bond formation assisted by carboxylic acids (Scheme 1, path a).[9] However, these reactions are often air- or moisture-sensitive, and stoichiometric Ag^I, $PhI(OR)_2$, or Cu^{II} reagents are usually required. Recently, copper-catalyzed oxidative protocols have shown to be powerful synthetic alternatives to these reactions.[10] As global demand and prices for noble metals continue to rise, however, chemists are being challenged to design metal-free processes. To this end, the use of well-defined I^{III} reagents has recently gained considerable momentum.[11] Although the generation of substantial aryl iodide (ArI) residues constitutes a significant barrier for the implementation of such protocols, early studies by the research groups of Kita, Ochiai, and Togo showed that catalytic amounts of ArI in the presence of suitable oxidants could be equally effective.[12] Despite further advances,[13] at the outset of our investigations, a C–H functionalization assisted by carboxylic acids and ArI catalysts en route to benzolactones did not have any literature precedents.[14] Herein, we describe a benign ArI-catalyzed process for C(sp^2)/C(sp^3)–H functionalization and C–O bond formation (Scheme 1, paths b and c). The method is user-friendly, operates with a wide substrate scope, occurs under mild conditions, and can be carried out in air. Initial studies showed an unprecedented and intriguing selectivity profile that can be easily modulated by the nature of the catalyst employed.[15]



Scheme 1. Synthesis of benzolactones by catalytic C–H functionalization.

We began our investigations by examining the reactivity of **1a**. After some experimentation,[16] we found that **I8** (20 mol %) in HFIP[17] with ACOOH as the oxidant enabled the synthesis of **2a** in nearly quantitative yield and in air at room temperature.[18,19] This finding is particularly remarkable and constitutes an additional bonus, practicality aside, when compared with related metal-catalyzed protocols.[7,8,10] Encouraged by these findings, we set out to explore the preparative scope of our surprisingly facile **I8**-catalyzed C(sp^2)–H functionalization/C–O bond-forming reaction (Scheme 2). As shown, the outcome was largely insensitive to changes in the electronic nature of the substrates. Thus, acetals (product **2c**), nitro groups (product **2e**), esters (products **2g**, **2j**, and **2l**), and aryl fluorides (product **2m**) were well accommodated. Similarly, non-aromatic carboxylic acids (product **2i**) or substrates prone to C(sp^3)–H functionalization (product **2h**) posed no problems. To put these results into perspective, we observed little conversion, if any, of **1c**, **1d**, or substrates bearing electron-withdrawing groups, such as **1e**, **1f**, **1j**, and **1l**, under previously developed copper-catalyzed conditions (Scheme 2).[10] Products **2k–n** were isolated as single regioisomers, and **2m** was unambiguously characterized by X-ray crystallographic analysis.[20] These results are in contrast with those of copper-catalyzed protocols, which invariably provide regioisomeric mixtures of these

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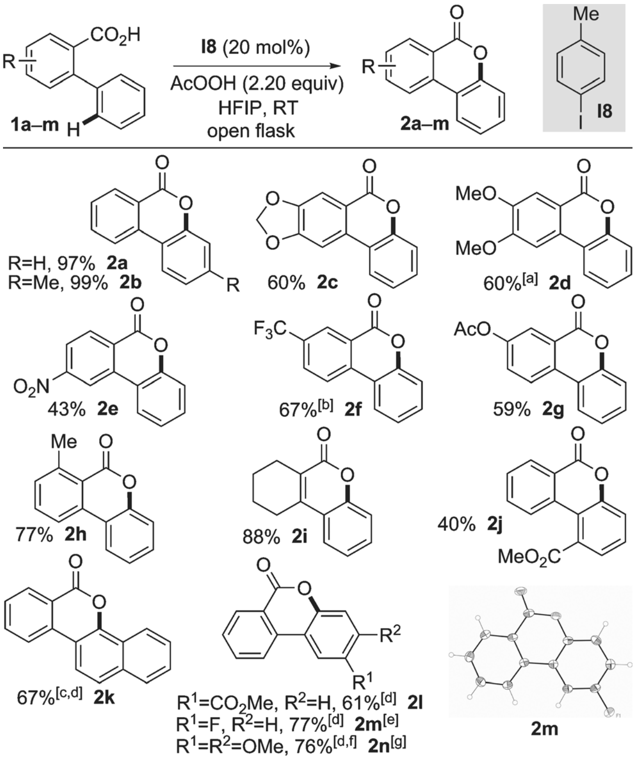
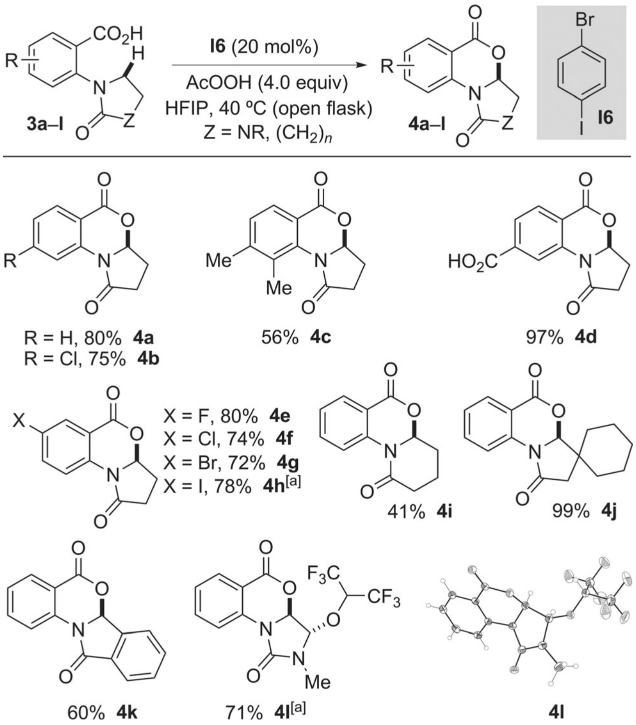


Scheme 2. C(sp^2)–H functionalization/C–O formation. Reaction conditions: **1** (0.20 mmol), **I8** (20 mol %), AcOOH (2.20 equiv), HFIP (1 mL), room temperature, 12 h. Yields given are for the isolated product and an average over two reactions. [a] The reaction was carried out with **I11** (20 mol %). [b] The reaction was carried out with AcOOH (4.40 equiv) at 80 °C. [c] The reaction was carried out with AcOOH (1.10 equiv). [d] The product was obtained as a single regioisomer. [e] The product was obtained as a 4:1 mixture of regioisomers under the conditions described in Ref. [10a]. [f] The reaction was carried out with PIFA (1.0 equiv). [g] The product was obtained as a 6:1 mixture of regioisomers under the conditions described in Ref. [10a]. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, PIFA = [bis(trifluoroacetoxy)iodo]benzene.

compounds.[10] We believe these results nicely illustrate the complementarity of **I8**- and copper-catalyzed oxidative processes.

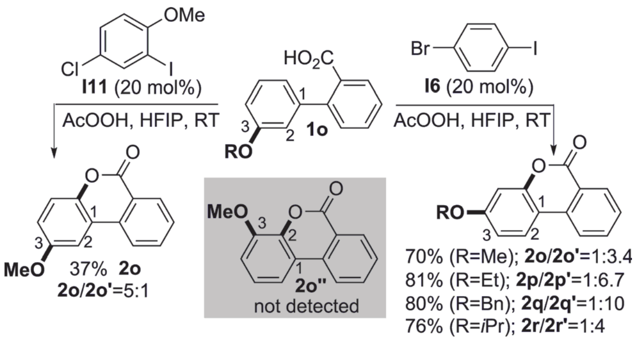
A closer look at the literature indicates that harsh conditions are typically required to prepare benzolactones by metal-catalyzed C(sp^3)–H functionalization with carboxylic acids as directing groups.[7,8d] Challenged by this finding, we wondered whether the mild protocol in Scheme 2 could be adapted to a C(sp^3)–H functionalization scenario.[21] We identified 5*H*-pyrrolo[1,2-*a*][3,1]benzoxazinones (**4**) as ideal targets to demonstrate the feasibility of such a concept, given the potential of these frameworks as lifespan-altering compounds and the ease of C(sp^3)–H functionalization α to the nitrogen atom (Scheme 3).[22] Among the catalysts tested, we found that **I6** was particularly competent for our purposes.[18,23] The method tolerated a variety of substitution patterns without significantly influencing the reaction outcome (Scheme 3). Interestingly, carboxylic acids (product **4d**) and aryl halides were tolerated (products **4b**,**e–h**), thus providing ample opportunity for cross-coupling techniques.



Scheme 3. C(sp^3)–H functionalization/C–O formation. Reaction conditions: as for Scheme 2, but with **I6** (20 mol %), at 40 °C, open to air. Yields given are for the isolated product and an average over two independent experiments. [c] The reaction was carried out with PIFA (2.5 equiv).

The preparation of **4j–l** indicates that five-membered rings other than pyrrolidinone can be equally effective. Similarly, pyridobenzoxazinones (**4i**) are also within reach. Interestingly, **4l** was obtained as a single diastereoisomer, the configuration of which was confirmed by X-ray crystallography.[24,25]

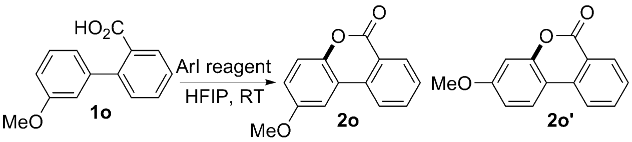
The observed influence of the ArI backbone suggested that site selectivity could be possible under appropriate conditions. We found an unprecedented catalyst-controlled selectivity switch when using **1o** (Scheme 4). Before process optimization, we found that the use of **I11** resulted in the formation of the expected product **2o** in 37 % yield together with a minor regioisomer, which was initially assigned as **2o″**. Careful NMR spectroscopic analysis, however, revealed that

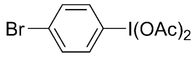
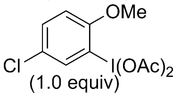


Scheme 4. Catalyst-controlled selectivity switch for the transformation of **1o–r**. Bn = benzyl.

our assignment was premature, and this minor regioisomer turned out to be **2o′**, a species not expected on the basis of simple selectivity between the two *ortho* C–H sites. Intriguingly, the use of structurally related **I6** resulted in a selectivity switch to give predominantly **2o′** in 70% yield.[26–28] This result might suggest that an incipient positive charge is developed on the electron-rich aromatic ring, thus triggering a [1,2]-aryl shift.[29] The structures of both **2o** and **2o′** were unequivocally established by X-ray crystallographic analysis (Scheme 4, top).[30] Importantly, the successful preparation of **2p′**, **2q′**, and **2r′** demonstrates the generality of this intriguing selectivity switch (Scheme 4, bottom).

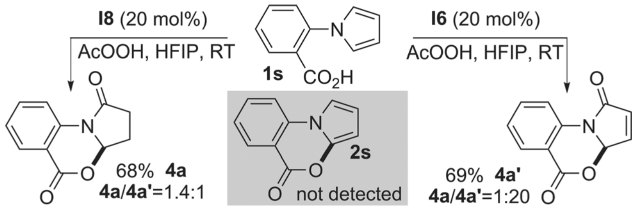
Next, we focused our attention on unraveling the origin of the selectivity switch shown in Scheme 4 by studying the reaction of **1o** with I$^{\rm III}$ reagents derived from **I6** and **I11**. Interestingly, we found that both **I6(OAc)$_2$** and **I11(OAc)$_2$** provided preferentially **2o′** (Scheme 5, entries 1 and 5), whereby **I6(OAc)$_2$** provided a slightly better selectivity profile (entry 1). These findings were rather surprising, since the **I6**- or **I11**-catalyzed event with AcOOH as the oxidant resulted in much lower **2o**/**2o′** ratios (entries 4, 7 and Scheme 4). We speculated that AcOOH might not be a mere spectator and could have dual roles, both as an oxidant and as a modulator at the I$^{\rm III}$ center. In line with this notion, the inclusion of AcOOH significantly eroded the selectivity profile with **I6(OAc)$_2$** (entries 2 and 3) or even caused a selectivity switch with **I11(OAc)$_2$** (entry 6). We believe these results tacitly suggest that the selectivity pattern is dictated by both the nature of the employed aryl iodide and the concentration of AcOOH. The role of the latter was nicely illustrated by careful analysis of the **2o′**/**2o** ratio as a function of time when using catalytic amounts of **I6**,[16] clearly showing that the concentration of AcOOH had a profound influence on the **2o′**/**2o** ratio. A similar behavior was observed for **PhI(1o)$_2$**, with which the presence of AcOOH had a deleterious effect on selectivity.[16] Overall, we believe that the results in Scheme 5 reveal an intimate interplay between the aryl iodide motif and the inclusion of noninnocent additives.[31]



Entry	ArI reagent	Additive (*x* equiv)	Yield [%]	**2o**/**2o'**
1		none	83	1:13.6
2		AcOOH (0.5)	75	1:5
3	(1.0 equiv)	AcOOH (2.0)	69	1:1.2
4	**I6** (20 mol%)	AcOOH (2.0)	74	1:3.4
5		none	75	1:10
6	(1.0 equiv)	AcOOH (2.0)	50	3:1
7	**I11** (20 mol%)	AcOOH (2.0)	37	5:1

Scheme 5. Unraveling of the observed selectivity profile for **1o**.

In light of these results, we wondered whether a related selectivity switch could be applied in another C–H functionalization event. Gratifyingly, we found that the transformation of **1s** followed a distinctive pattern when **I6** or **I8** were used as catalysts (Scheme 6).[31,32] While one might have anticipated that **1s** would trigger a C(sp^2)–H functionalization en route to **2s**, this was not the case, and **4a** or **4a′** were obtained exclusively, as ultimately confirmed by X-ray crystallographic analysis.[33,34] Whether these observations indicate a general trend for other substrate combinations or there are other mechanistic implications is the subject of ongoing studies in our laboratories.



Scheme 6. Catalyst-controlled selectivity switch for the transformation of **1s**.

In summary, we have developed a C(sp^2)–H or C(sp^3)–H functionalization/C–O bond-forming process catalyzed by I$^{\rm III}$ reagents generated in situ. The reaction occurs under mild conditions and with an intriguing selectivity switch depending on the catalyst used. This air-insensitive method is a cheap and practical alternative to related metal-catalyzed protocols. Further investigations into related processes are currently ongoing.

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[19] Low yields of **2a** were found with 4-iodobenzaldehyde (29 %), 4-iodobenzoic acid (14 %), I_2 (40 %), and KI (22 %). These results suggest that the reactivity of **I8** cannot be merely attributed to the oxidation of the benzylic C–H bond in **I8** or degradation into inorganic iodine compounds.

[20] CCDC 1012792 (**2m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[23] No reaction took place when *N*-phenylpyrrolidinone was exposed to benzoic acid in the presence of a catalytic amount of **I6**. A similar result was observed when the methyl ester of **3a** (**3a**-Me) was used.

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[27] The reaction of **1o** with **I8** or PhI (**I1**) as catalysts gave rise to a mixture of **2o** and **2o′** in 67 and 56 % yield (**I8:** 1:1.7 ratio; **I1**: 1:1.2 ratio), thus clearly demonstrating the influence of the aryl backbone on selectivity. For the use of other ArI catalysts, see the Supporting Information.

[28] Control experiments showed that **2o** and **2o′** cannot be interconverted.

[29] For selected [1,2]-carbon-atom shifts promoted by PhI(OR)$_2$, see: a) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem.* **2013**, *125*, 7156; *Angew. Chem. Int. Ed.* **2013**, *52*, 7018; b) K. Hata, H. Hamamoto, Y. Shiozaki, S. B. Cämmerer, Y. Kita, *Tetrahedron* **2007**, *63*, 4052. In these examples, the nature of the ArI(OR)$_2$ reagent employed had minimal influence on selectivity.

[30] CCDC 1012788 (**2o**) and 1012789 (**2o′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[31] The influence of the ArI backbone can be attributed to a greater electrophilicity of the I$^{\text{III}}$ species generated from **I6** in comparison to those generated from **I11** or **I8**.

[32] The exposure of **1s** to previous copper-catalyzed oxidative conditions[10] gave neither conversion into **4a**, **4a′** nor into **2s**.

[33] Compound **1s** was cleanly converted into either **4a** or **4a′** in an Ar atmosphere, thus suggesting that atmospheric oxygen does not come into play.

[34] CCDC 1012793 (**4a**) and 1012790 (**4a′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.