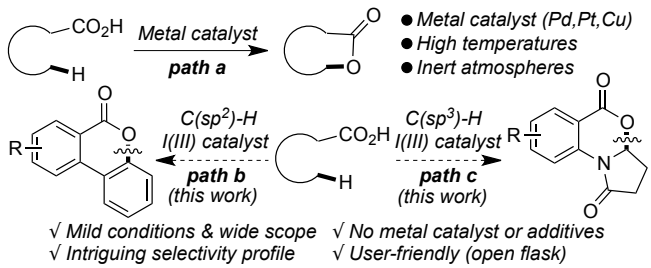
A Mild ArI-catalyzed C(sp^2)– and C(sp^3)–H Functionalization/C–O Formation: An Intriguing Catalyst-controlled Selectivity Switch

Xueqiang Wang[a], Joan Gallardo-Donaire[a] and Ruben Martin*[a,b]

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

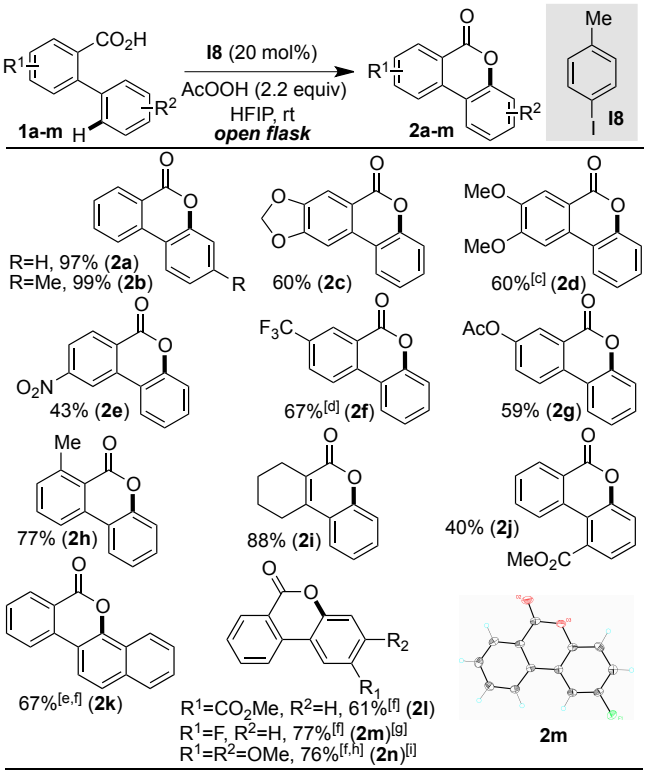
The recent years have witnessed a dramatic progress in the field of C–H functionalization, allowing the design of unconventional synthetic strategies.[1] While a myriad of catalytic C–C and C–N bond-formation have been developed, the means to effect a C–O bond-formation has received much less attention.[2] This is in part due to the large energy gap between the M–O HOMO and M–C LUMO frontier orbitals.[3] Thus, the development of an innovative, yet practical, C–H functionalization/C–O bond-formation has become a goal for synthetic chemists. [4,5] The preparation of benzolactones represents an ideal target since compounds such as Lamellarin or Cytosporone, among others, show attractive biological properties. [6]



Scheme 1. Benzolactones via catalytic C-H functionalization.

We[7] and others[8] have reported the synthesis of benzolactones via Pt- or Pd-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, Cu-catalyzed oxidative protocols have shown to be powerful synthetic alternatives to these endeavors. [10] As global demand and prices for noble metals continue to rise, however, chemists are being challenged to design metal-free processes. To such end, the use of well-defined I(III) reagents has recently gained considerable momentum at the Community.[11] Although the generation of substantial aryl iodide (ArI) residues constitute a significant barrier for the implementation of such protocols, early work by Kita, Ochiai and Togo showed that catalytic amounts of ArI in the presence of suitable oxidants could be equally effective.[12] Despite the advances realized, [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 C(sp^2)– and C(sp^3)–H functionalization/C–O bond-formation (Scheme 1, paths b and c). The method is user-friendly, operates with a wide substrate scope under mild conditions, and in open-air. Initial studies show an unprecedented and intriguing selectivity profile depending on the nature of the catalyst employed. [15]

Table 1. C(sp^2)–H Functionalization/C–O formation. [a,b]



[a] Reaction conditions: **1** (0.20 mmol), **I8** (20 mol%), AcOOH (2.20 equiv), HFIP (1 mL) at rt for 12 h. [b] Isolated yields, average of two runs. [c] I11 (20 mol%). [d] AcOOH (4.40 equiv), 80 ºC. [e] AcOOH (1.10 equiv). [f] Single

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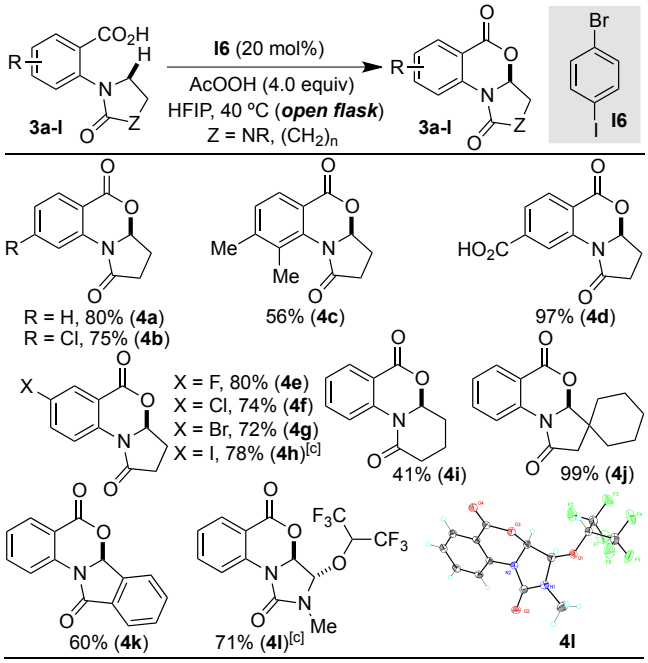
regioisomer. [g] 4:1 regioisomers under conditions of Ref. 10a. [h] PIFA (1.0 equiv). [i] 6:1 regio- isomers under conditions of Ref. 10a.

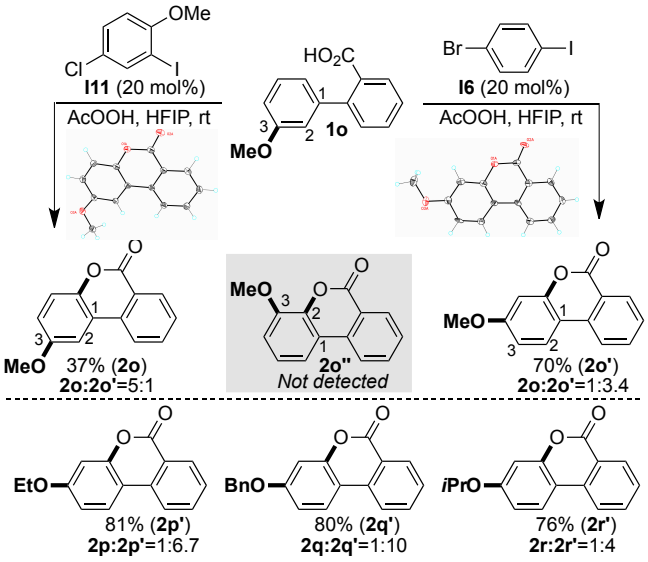
We began our investigations by examining the reactivity of **1a**. After some experimentation,[16] we found that **I8** (20 mol%) in HFIP[17] and ACOOH as the oxidant allowed for obtaining **2a** in nearly quantitative yield and in open air at rt. [18,19] Such finding is particulary remarkable, thus constituting 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-formation (Table 1) As shown, the outcome was largely insensitive to changes in the electronic nature of the substrates. Thus, acetals (**2c**), nitro groups (**2e**), esters (**2g**, **2j** and **2l**) and aryl fluorides (**2m**) were well accommodated. Similarly, non-aromatic carboxylic acids (**2i**) or substrates prone to C(sp^3)–H functionalization (**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 Cu-catalyzed conditions (Table 1). [10] Interestingly, **2k**-**2n** were isolated as single regioisomers, with **2m** unambiguously characterized by X-ray analysis.[20] These results are in sharp contrast with Cu-catalyzed protocols that invariably provide regioisomeric mixtures of these compounds. [10] We believe these results nicely illustrate the complementarity of **I8**- and Cu-catalyzed oxidative processes.

Table 2. C(sp^3)–H Functionalization/C–O formation.[a,b]



[a] Conditions: As for Table 1, but using **I6** (20 mol%), at 40 ºC, open to air. [b] Isolated yields, average of two independent runs. *c* PIFA (2.5 equiv).

A closer look into the literature indicates that harsh conditions are typically required to prepare benzolactones via metal-catalyzed C(sp^3)–H functionalization using carboxylic acids as directing groups. [7,8d] Challenged by such finding, we wondered whether the mild protocol in Table 1 could be adapted to a C(sp^3)–H functionalization scenario.[21] To such end, we identified 5*H*-pyrrolo-[1,2-*a*][3,1]benzoxazinones (**4a**) as an ideal target to demonstrate the feasibility of such concept given the potential of these frameworks as lifespan-altering compounds and the ease for C(sp^3)–H functionalization α to the nitrogen atom (Table 2). [22] Among all catalysts utilized, we found that **I6** was particularly competent for our purposes. [18,23] As shown in Table 2, the method tolerated a variety of substitution patterns without significantly influencing the reaction outcome. Interestingly, remote carboxylic acids (**4d**) or aryl halide entities were tolerated (**4b** and **4e-h**), leaving ample opportunities for subsequent manipulation via cross-coupling techniques. The successful preparation of **4j-4l** indicates that five-membered rings other than pyrrolidinone can be equally effective. Similarly, pyrido-benzoxazinones (**4i**) are also within reach, albeit in lower yields. Interestingly, **4l** was obtained as a single diastereoisomer, whose stereochemistry was confirmed by X-ray crystallography.[24,25] Taken together, we believe the results in Tables 1-2 improve significantly the practicality of catalytic C(sp^2)– and C(sp^3)–H functionalization/C–O bond-formation protocols assisted by carboxylic acids.

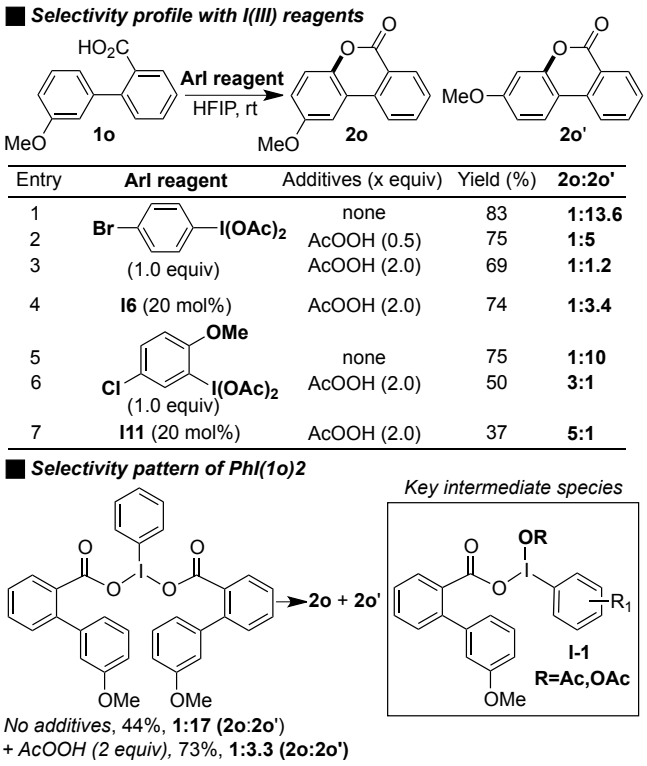


Scheme 2. Catalyst-controlled Selectivity Switch for **1o**.

The observed influence of the ArI backbone suggested that site-selectivity could be accomplished under appropriate conditions. As shown in Scheme 2, we found an unprecedented catalyst-controlled selectivity switch when using **1o**. Although not yet fully optimized, we found that the use of **I11** resulted in 37% yield of the expected **2o** together with a minor regioisomer that was initially assigned as **2o''**; a careful NMR spectroscopical analysis, however, revealed that our assignment was premature and such *minor regioisomer turned out to be* ***2o'****, a species not*

expected through a simple selectivity between the two ortho C–H sites. Intriguingly, structurally related **I6** resulted in a selectivity switch, obtaining 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 assignment of both **2o** and **2o'** was univocally established by X-ray analysis (Scheme 2, top).[30] Importantly, the successful preparation of **2p'**, **2q'** and **2r'** demonstrates the generality of such intriguing selectivity switch (Scheme 2, bottom).

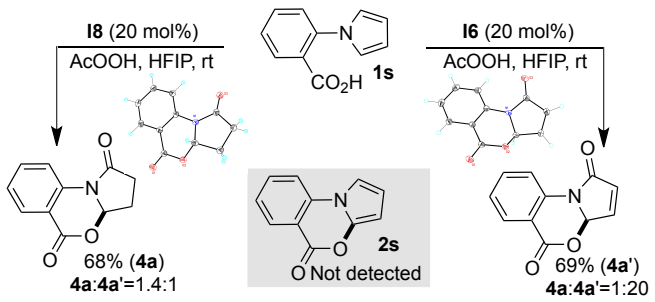
Next, we focused our attention on unraveling the origin of the selectivity switch shown in Scheme 2 by studying the reaction of **1o** with I(III) reagents derived from **I6** and **I11**. Interestingly, we found that both **I6(OAc)$_2$** and **I11(OAc)$_2$** provided preferentially **2o'** (Scheme 3, entries 1 and 5), with **I6(OAc)$_2$** providing a slightly better selectivity profile (entry 1). These findings were rather surprising since the **I6-** or **I11-**catalyzed event using AcOOH as the oxidant resulted in a much lower **2o:2o'** ratios (entries 4, 7 and Scheme 2). We speculated that AcOOH might not be a mere spectator and that could be acting with dual roles, both as an oxidant and as a modulator at the I(III) center. In line with this notion, the inclusion of AcOOH significantly eroded the selectivity profile using **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 [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 evidencing that the [AcOOH] had a profound influence on the **2o':2o** ratio. A similar behavior was observed for **PhI(1o)$_2$** (Scheme 3, bottom left), one of the potential reaction intermediates, in which the presence AcOOH had a deleterious effect on selectivity. Overall, we believe the results in Scheme 3 suggest the intermediacy of **I-1** species within the catalytic cycle (Scheme 3, bottom right), revealing an intimate interplay between the aryl iodide motif and the inclusion of non-innocent additives.



Entry	ArI reagent	Additives (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 3. Unraveling the Observed Selectivity Profile for **1o**.

In light of these results, we wondered whether a related selectivity switch could be applied in other C–H functionalization event. Gratifyingly, we found that **1s** followed a distinctive pattern when using **I6** or **I8** as catalysts (Scheme 4).[31] 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, an assumption that was ultimately confirmed by X-ray analysis. [32,33] Whether these observations indicate a general trend in other substrate combinations or if it has other mechanistic implications is matter of ongoing studies.



Scheme 4. Catalyst-controlled Selectivity Switch for **1s.**

In summary, we have developed a C(sp^2)– and C(sp^3)–H functionalization/C–O bond-formation event catalyzed by *in situ* generated hypervalent I(III) reagents. The reaction occurs under mild conditions and with an exquisite and intriguing selectivity profile that can be switched depending on the catalyst

employed. This new air-insensitive method represents a cheap, practical, and a powerful alternative to related metal-catalyzed protocols. Further investigations into related processes are currently ongoing.

Acknowledgements

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Keywords: metal-free • catalysis • site-selectivity• C-H functionalization •

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

[20] CCDC 1012792 (**2m**) contain the supplementary crystallographic data for this paper and 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 exposing N-phenylpyrrolidinone with benzoic acid under catalytic amounts of **I6**. A similar result was observed when using the methyl ester of **3a** (**3a**-Me).

[24] CCDC 1012791 (**4I**) contain the supplementary crystallographic data for this paper and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac/uk/data_request/cif

[25] The formation of **4I** is consistent with the formation of iminium ions. Such assumption goes in line with the ease for C(sp^3)-H oxidation α to nitrogen in amines. See for example a related contribution using I(III) reagents and azides: P. Magnus, C. Hulme, W. Weber, *J. Am. Chem. Soc.* **1994**, *116*, 4501.

[26] For a mechanistic hypothesis, see Supporting Information.

[27] The reaction of **1o** with I**8** or PhI (**I1**) as catalysts gave rise to a mixture of **2o** and **2o**' in 67% and 56% yield, with a 1:1.7 ratio for **I8** and 1:1.2 ratio for **I1** (**2o**:**2o**') These results reinforce the notion that the ArI motif exerts an influence on selectivity. For the use of other ArI catalysts, see supporting information.

[28] Control experiments showed that **2o** and **2o**' cannot be interconverted, suggesting two distinctive mechanistic scenarios.

[29] For selected [1,2]-carbon shifts promoted by stoichiometric amounts of $PhI(OR)_2$: (a) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem., Int. Ed.* **2013**, *52*, 7018. (b) K. Hata, H. Hamamoto, Y. Shiozaki, S. B. Cämmerer, Y. Kita, *Tetrahedron* **2007**, *63*, 4052. (c) A.

C. Boye, D. Meyer, C. K. Ingison, A. N. French, T. Wirth, *Org. Lett.* **2003**, *5*, 2157. Interestingly, in these examples the nature of the $ArI(OR)_2$ employed had a minimum influence on selectivity, thus showing the distinctive features of our method.

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

[31] Exposure of **1s** under previous Cu-catalyzed oxidative conditions (ref. 10) gave neither conversion to **4a**, **4a**' nor to **2s**.

[32] Control experiments indicated that **1s** was cleanly converted to either **4a** or **4a**' in Ar atmospheres, thus suggesting that atmospheric oxygen does not come into play.

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

COMMUNICATION

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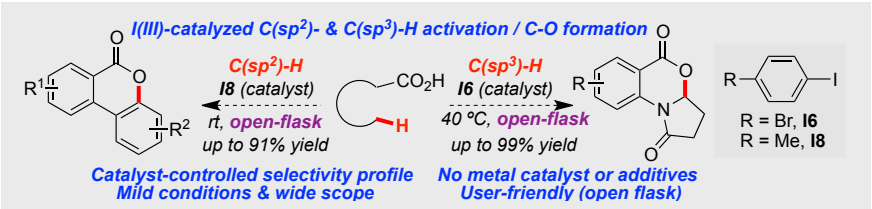
Title



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