An Intramolecular Iodine-Catalyzed C(sp³)–H Oxidation as a Versatile Tool for the Synthesis of Tetrahydrofurans

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In memory of the early death of Kilian Muñiz.

The formation of ubiquitous occurring tetrahydrofuran patterns has been extensively investigated in the 1960s as it was one of the first examples of a non-directed remote C–H activation. These approaches suffer from the use of toxic transition metals in overstoichiometric amounts. An attractive metal-free solution for transforming carbon-hydrogen bonds into carbon-oxygen bonds lies in applying economically and ecologically favorable iodine reagents. The presented method involves an intertwined catalytic cycle of a radical chain reaction and an iodine(l/III) redox couple by selectively activating a remote C(sp³)–H bond under visible-light irradiation. The reaction proceeds under mild reaction conditions, is operationally simple and tolerates many functional groups giving fast and easy access to different substituted tetrahydrofurans.

The formation of saturated heterocycles by C–H activation of unactivated C(sp³)–H bonds can look back on a long history of extensive research[1] and be first discovered by Hofmann in the late 1800s for pyridines.[2] His approach was based on forming highly reactive nitrogen-centered radicals from the homolysis of haloamines, activating distant carbon-hydrogen bonds by an intramolecular 1,5-hydrogen atom transfer (HAT).[3,4,5,6] The synthetic value of this reaction was demonstrated more than 25 years later by the elegant synthesis of nicotine by Löffler and Freytag.[7] Analogous reactions based on oxygen radicals were developed a little later, enabling valuable access to tetrahydrofurans (THF). The THF motifs can be found in various natural products and play a crucial role in terpenes and steroids, where THF rings were also introduced as “intermediates” to install an oxygen-functionality to an unactivated methyl group.[8] Alkoxyl radicals initiate this intramolecular remote functionalization of non-activated atoms prepared in-situ by different procedures (Scheme 1).[9] For example, they can be generated by the photolysis of nitrite esters (Barton reaction).[10] Alternatively, O-centered radicals were prepared in-situ via a hypoiodite reaction with heavy metals such as lead tetraacetate (LTA) or by less toxic reagents like an N-iodosuccinimide or (diacetoxyiodo)benzene (DIB) (Suárez modification).[11] However, an excess of the oxidizing reagent and equimolar amounts of molecular iodine is required, also leading to undesired overoxidation products.[12] A few years ago, the Togo group reported the synthesis of heterocycle using diiodohydantoins.[13] Recently, the group of Muñiz overcame these drawbacks for the synthesis of pyrrolidines and presented an iodine-catalyzed version of the Hofmann-Löffler reaction using different oxidants and light sources such as DIB analogs,[14] m-CPBA with t-BuOH[15] or TPT with H₂O and irradiation with blue LEDs.[16] Inspired by this reaction protocol’s simplicity and efficacy, we envisioned developing an iodine-catalyzed, remote C–H activation of primary and secondary alcohols to access tetrahydrofurans under mild reaction conditions easily.

We commenced our investigations on the steroidal alcohol 3β-acetoxy-2β-hydroxy-5α-androstan-17-one (1a), the key intermediate in the semi-synthesis towards the cardiac glycoside Calotropin.[17,18] Due to the rigid steroidal skeleton, the hydroxyl group and the methyl group to be activated are close to one another, facilitating the C–H activation and the formation of the THF ring (Table 1). Suárez-type reaction conditions with stoichiometric amounts of iodine, commercially available DIB, and...
irradiation with a 500 W halogen lamp were applied to deliver the product 1b in a moderate yield of 46% (entry 1). Upon lowering the amount of iodine to 10 mol%, a similar yield of 44% was obtained (entry 2). Changing the iodine(III) reagent to PhI(m-CBA)2 (m-CBA = 3-chlorobenzoate) under otherwise identical catalytic reaction conditions provided product 1b with a very good yield of 77% (entry 3).

When lowering the amount of iodine to 5 mol%, the reaction seems to proceed slower, giving the product in 35% yield (entry 4). The reaction can also be carried out at room temperature and exposure to daylight with PhI(m-CBA)2 as oxidant, with the same yield under artificial irradiation (entries 5 and 6). Even though the cyclization reaction works better with stoichiometric amounts of iodine (entry 5), affording the product with 78% yield, good yields of 60% were also isolated with catalytic amounts of iodine (entry 6). Nevertheless, the reaction seems to proceed slower and require longer reaction times. No further optimization could be achieved by fine-tuning the electronic properties of iodine(III) reagents. Neither by changing the substituents on the aryl moiety to a more electron-withdrawing nor an electron-donating substituent had the desired effect (entries 7–9). With the presented cyclization reaction, the need for an excess of a terminal oxidant is no longer required. In combination with the use of catalytic amounts of iodine, this results in a much cleaner reaction outcome than comparable protocols leading to overoxidation. Without either iodine (entry 10) or light (entry 11), no conversion of the starting material was detected. Additionally, the reaction can also be conducted with defined LED irradiation (see ESI chapter 2.3.3), but to keep the reaction set-up operationally simple, we preferred using a simple halogen lamp as a light source.

As previously reported for iodine-catalyzed Hofmann-Löffler reactions,[18] it is initiated by the formation of the active catalyst I(mCBA) from molecular iodine and the hypervalent iodine(III) reagent (Scheme 2). We propose the in-situ formation of a hypoiodite accompanied by the formation of the corresponding carboxylic acid m-CBAH. Contrary to the results of the Muñiz group, which showed a stabilizing effect of carboxylic acid by the formation of I(m-CBA) · m-CBAH adduct,[14] we detected a slight drop in yield in the presence of five equivalents of m-CBAH (Table 1, entry 12) indicating that in our case the free carboxylic acid influences the reaction mechanism. However, the photochemical decomposition of the alkoxy radical gives

Table 1. Development of the iodine-catalyzed cyclization reaction.

| Entry | Oxidant     | I2 (x [mol%]) | Conditions | Yield [%][a] |
|-------|-------------|---------------|------------|--------------|
| 1     | PhI(OAc)2   | 100           | 9 h, 500 W lamp, 45 °C | 46[10]    |
| 2     | PhI(OAc)2   | 10            | 9 h, 500 W lamp, 45 °C | 44[10]    |
| 3     | PhI(m-CBA)2 | 10            | 9 h, 500 W lamp, 45 °C | 77         |
| 4     | PhI(m-CBA)2 | 5             | 9 h, 500 W lamp, 45 °C | 35[10]    |
| 5     | PhI(m-CBA)2 | 100           | 2 d, day light, rt | 78         |
| 6     | PhI(m-CBA)2 | 10            | 2 d, day light, rt | 60         |
| 7     | PhI(m-DCBA)2| 10            | 9 h, 500 W lamp, 45 °C | 78         |
| 8     | PhI(m-DMBA)2| 10            | 9 h, 500 W lamp, 45 °C | 60         |
| 9     | PhI(PFBA)2  | 10            | 9 h, 500 W lamp, 45 °C | 68         |
| 10    | PhI(m-CBA)2 | 0             | 9 h, 500 W lamp, 45 °C | 0          |
| 11    | PhI(m-CBA)2 | 10            | 9 h, darkness, 45 °C | 0          |
| 12    | PhI(m-CBA)2 | 10            | 9 h, 500 W lamp, 45 °C | 60[10]    |

[a] Yields refer to isolated material of 1b after purification. [b] Starting material was recovered. [c] Reaction in the presence of 5.0 equiv. m-CBAH.

Scheme 2. Proposed reaction mechanism for the iodine-catalyzed cyclization reaction.
the O-centered radical that can abstract a hydrogen atom from a spatially close C–H group in δ-position, in this case, the C-19 methyl group. After recombination of the radicals, the carbon atom is oxidized by the hypervalent iodine(III) reagent followed by a nucleophilic attack of the 2-hydroxy group, which is due to the increased leaving group ability of iodine(III) comparatively fast (e.g., compared with the direct oxygenation) resulting in the formation of the THF ring and the regeneration of the active catalyst.

Next, we were keen to explore whether the reaction can be extended to aliphatic substrates with flexible structures whose hydroxyl groups are not close to the activated C–H bond (Scheme 3). For this purpose, we started our investigations with aliphatic alcohols of different lengths ranging from 1-decanol to 1-docosanol. Gratifyingly, the same reaction procedure proved applicable to non-pre-oriented aliphatic alcohols giving the corresponding products after column chromatography on silica gel in good yields ranging from 58% to 79% (2b–5b).

The formation of the corresponding tetrahydropyran (THP)-product was not observed to the best of our knowledge, indicating that the reaction favors the formation of 5-membered cycles over 6-membered cycles. The cyclization reaction of 1-decanol was monitored by analyzing reaction aliquots via 1H NMR spectroscopy (see ESI, Figure 1). The reaction follows second-order kinetics, and after 3 h, a steady-state is reached. When the missing amounts of PhI(m-CBA)2 

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**Scheme 3.** Competition experiments. Conditions: PhI(m-CBA)2 (1.0 equiv.) 10 mol% I2, 1,2-DCE, 45 °C, 500 W lamp. [a] 1.0 equiv. I2.
combined with additional 10 mol% iodine were added to achieve complete conversion, no starting material was left after another hour of irradiation at the latest. To investigate the substrate scope in more detail, branched alcohols were included in our studies, allowing different substitution patterns on the THF motif. As a consequence of the radical reaction mechanism of the cyclization, no diastereoselectivity was observed giving the 2,5-substituted THF moieties, unbranched and branched secondary alcohols were successfully subjected to the reaction to access 2,5-substituted THF moieties, unbranched and branched secondary alcohols were successfully subjected to the reaction to achieve complete conversion, no starting material was left after 16 h. Yields were determined after purification by column chromatography on silica gel. The newly formed C–O bonds are highlighted in red. * 1.0 equiv. I₂ was used.

Activation of a benzylic position was also feasible as it was shown for 14b (48%) whereby functional groups such as a methoxy group (15b: 47%) or a bromo residue (16b: 48%) were well tolerated at the aromatic without any impact on the yield. To further explore the tolerance towards functional groups, substituted alkyl chains were examined. We commenced with common OH-protecting groups such as alkyl-, benzyl-, or silyl ether and an acetyl protecting group, all of which give the corresponding products in moderate yields (19b: 37% (Me), 20b: 43% (SiR₃), and 21b: 46% (Ac). When stoichiometric amounts of iodine were applied, an increase in yield was observed, as demonstrated for 21b (75%), showing that the functional groups impact the turnover of the cyclization. By augmenting the distance between the δ–C–H bond and the functional group, yields could be in some cases augmented as shown for 26b: 50% (OMe) and 27b: 62% (Ac) while the corresponding benzyl protected alcohol 28b was obtained in similar yields of 46% (OOb). When stoichiometric amounts of I₂ were used, no significant improvements in yield were observed. In comparison, lower yields were obtained for alcohols containing a tosyl (22b: 34%), a cyano (23b: 42%), an ester (24b: 37%) or carboxyl group (25b: 31%). We were happy to see that a phthalimide containing alcohol was also well tolerated affording the THF-product 29b in 54% yield.

A benzylic C–H-bond next to oxygen was successfully activated, giving the corresponding 1,3-dioxolane 17b in 56% yield. When blocking the δ-position of the alcohol with an oxygen atom, as is the case for 3-(benzyloxy)propanol, the formation of the corresponding 6-membered cycles occurred, affording the 1,3-dioxane product 18b in 67% yield.

This result motivated us to conduct competition experiments to understand better the reactivity of alcohols bearing two competing reaction sites (Scheme 3). As a result, we demonstrated that even in the presence of a more activated, benzyl C–H-bond, only the formation of the 5-membered THF ring is observed, implying the entropic control of the reaction (experiment 1; 30b: 40%). The corresponding THP-product 30c was not formed in detectable amounts. Furthermore, the cyclization reaction favors the activation of secondary C–H-bonds over primary C–H-bonds in aliphatic alcohols as exclusively the more electron-rich secondary C–H-bond was attacked as showcased for 4-undecanol (31a), giving 31b even though only in 36% yield (experiment 2). In the absence of an aliphatic secondary C–H bond, an aromatic C–H bond is activated even if this causes the formation of the generally unfavored 6-membered THF-ring, even in the presence of a primary δ–C–H bond (experiment 3 and 4).

Noteworthy, the formation of 2,3-dihydrobenzo[2][5]furan has never been observed, not even in therefore designed substrates. In the presence of an aliphatic secondary C–H bond, its activation occurs again preferentially, and the THF-products 34b and 35b were isolated in 37% (34b) and 58% yield (35b) (experiment 5 and 6). Again, the usage of stoichiometric amounts of I₂ showed no impact on the yield in the cyclization of 34a. Interestingly, for the primary alcohol 36a comprising three different potentially addressable C–H bonds, the opposite behavior was observed as chromane 36c was detected (experiment 7). This observation was attributed to the steric demand of the residues at the C-3 hindering the attack by the hyper-valent iodine reagent as both 13b and 17b were successfully built in good yields (Scheme 3).

Next, we investigated if 1,n-diols (n=6–12) can undergo double C–H activation and whether any trend is detectable (Figure 2). In most cases, a double C–H-activation took place, but for 1,6-hexanediol and 1,8-octanediol, we could only isolate the mono-cyclized products (see ESI), which might also be due to the high volatility of the double-cyclized products. Gratifyingly, we were able to detect 37bb despite its low boiling point (48–52 °C/12 mmHg) when column chromatography was conducted with low-boiling solvents and if those were not...
place, affording the corresponding diastereomeric products. The product could not be isolated anymore. The amount of iodine and/or oxidant – on the contrary, the yield could not be improved by using higher amounts of iodine. Theworthy, the yield could not be improved by using higher amounts of iodine. The reaction progresses under mild conditions involving radicals, the reaction proceeds under mild conditions and is therefore of a broad substrate scope tolerating multiple H groups are accessible. Note-* the hydroxyl group and the methyl group are in close proximity. This supports that oxidization of the primary C–H bond is feasible if the hydroxyl group and the methyl group are in close proximity.

We have presented the first iodine-catalyzed synthesis for different substituted tetrahydrofurans through an intramolecular C(sp^3)–H oxidation of non-activated remote C(sp^3)–H bonds. The reaction proceeds under high regioselectivity favoring the formation of the 5-membered rings over the thermodynamically more stable 6-membered rings. This method requires only a single equivalent of oxidant per activated C–H bond, is operationally simple, and can be initiated either by daylight or a simple halogen lamp. The proposed reaction mechanism is based on two intertwined catalytic cycles combining a radical chain reaction with an iodine(I/III) redox couple. Although involving radicals, the reaction proceeds under mild conditions and is therefore of a broad substrate scope tolerating multiple functional groups that also allow further derivatization of the constructed THF-containing products. Aliphatic primary and secondary alcohols can be cyclized and aliphatic 1,2-diols giving access to molecules with one or two THF moieties. The disclosed method demonstrates the potential of iodine catalysis as a non-toxic and powerful alternative for the conventional metal-catalyzed synthesis of tetrahydrofurans.¹⁹

**Conflict of Interest**

The authors declare no conflict of interest.

**Keywords:** C–H functionalization · Iodine catalysis · Oxidation · Steroids · Tetrahydrofuran

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43 b in a 3:1 mixture in 38% total yield (Figure 4). These results support that oxidation of the primary C–H bond is feasible if the hydroxyl group and the methyl group are in close proximity.

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**Figure 2.** Reaction of 1,2-diols (n = 6–12) under light-induced iodine-catalyzed cyclization reaction conditions: I\(_2\) (10 mol%), PhI(m-CBA)\(_2\) (1.0 or 2.0 equiv.), 1,2-DCE, 45 °C, 16 h. Yields were determined after purification by column chromatography on silica gel. The newly formed C–O bonds are highlighted in red. x = 2–7; nd = not determined. More examples (n = 6, 8) can be found in the ESI.

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**Figure 4.** Derivatization of (+)-menthol (43 a).

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**Figure 3.** Exploitation of the substrate scope towards steroids based on the frameworks of androstone (1 b), corticosterone (41 b), and pregnenolone (42 b).
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