Oxidative decarboxylative ammonium hypoiodite-catalysed dihydrobenzofuran synthesis†

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The catalytic use of quaternary ammonium iodides under oxidative conditions allows for the direct conversion of readily available β-ketolactones into dihydrobenzofurans *via* a decarboxylative oxidative cycloetherification sequence facilitated by an *in situ* formed ammonium hypoiodite species.

The catalytic use of (chiral) quaternary ammonium iodides under oxidative conditions has emerged as a powerful concept within the broader field of hypervalent iodine-mediated and -catalysed transformations over the last few years.[1–3] The increasing research focus on this unique organocatalysis principle has led to the introduction of several valuable racemic as well as enantioselective transformations that are otherwise not easily possible with classical strategies.[2–10] Depending on the reaction conditions, oxidation of the iodide counter anion to different catalytically active higher oxidation state species (I_3, IO_n^-) can be achieved, amongst which ammonium hypoiodite derivatives $R_4N^+IO^-$ have been the most commonly postulated (and detected) catalytically relevant ones (simple oxidants like H_2O_2, oxone, or organic hydroperoxides can be used therefore) (Scheme 1A). These *in situ* formed species then allow for the oxidative Umpolung of the inherent reactivity of suited substrates (*e.g.* enolates can thus be rendered electrophilic in the α-position). The successful implementation of this concept allows for efficient (asymmetric) heterofunctionalizations as well as C–C bond forming reactions by utilizing easily accessible building blocks and a variety of impressive recent developments have been reported.[6–9] Ishihara's group contributed to the field like no other,[6–8] and in 2010 they reported the enantioselective oxidative cycloetherification of phenol derivatives 1, giving access to valuable dihydrobenzofuran (*n* = 1) or chroman (*n* = 2) derivatives 2 (Scheme 1B).[6] Key to high enantioselectivities was the installation of the imidazole group

in combination with a thoroughly optimized chiral Maruoka-type ammonium iodide catalyst.[6,11]

These seminal contributions sparked our interest in this concept and we have recently contributed by introducing an asymmetric ammonium hypoiodite catalysed α-hydroxylation of β-ketoesters.[10] In addition, and based on our general interest in the synthesis of dihydrobenzofuran derivatives as well,[12] we now became interested in introducing an alternative strategy to access diversely functionalized dihydrobenzofurans 5 starting from easily accessible lactones 4 (Scheme 1C). By utilizing these starting materials, we reason that it should be possible to carry out an efficient tandem decarboxylation-cycloetherification sequence, facilitated and controlled by quaternary ammonium iodide catalysts under oxidative conditions. The use of lactones 4 provides a complementary and
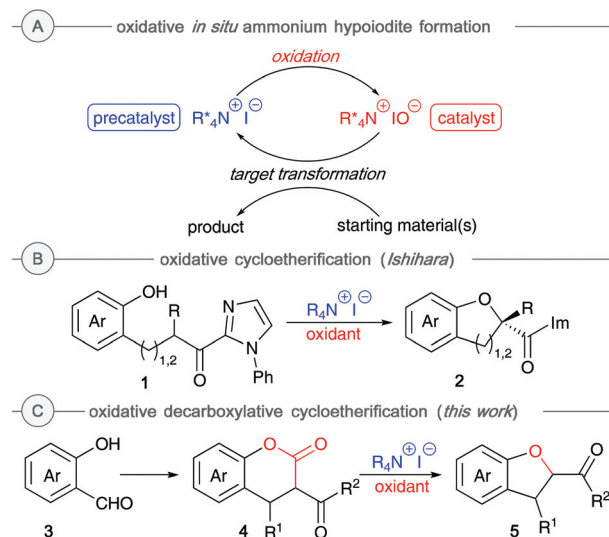
Scheme 1 *In situ* formation of catalytically competent ammonium hypoiodite species (A), Ishihara's seminal cycloetherification protocol (B), and the herein investigated decarboxylative cycloetherification approach (C).

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appealing alternative due to their straightforward availability from commercial salicylaldehyde derivatives **3** in two routine steps (tandem Knoevenagel condensation–lactonization followed by 1,4-hydrogenation or addition of C-nucleophiles),[13] thus avoiding a lengthy starting material synthesis. In addition, this sequence will also allow for the installation of benzylic R^1 substituents which will thus broaden the general application scope of the methodology.

We started our investigations by focusing on the use of β-ketolactone **4a** as a starting material (Table 1). First experiments utilizing tetrabutylammonium iodide (Bu₄NI) in combination with H₂O₂ (35% aq.) gave promising results (entries 1–3) as the use of a slight excess of H₂O₂ in combination with 30 mol% of the ammonium iodide catalyst allowed for the synthesis of product **5a** in 63% yield (accompanied with the formation of unidentified side-products). Utilizing the analogous ammonium bromide and chloride proved the necessity for the iodide counter anion, as no product was formed in these cases (entries 4 and 5). Testing alternative preformed hypervalent iodine-based ammonium salts (entries 6 and 7) as stoichiometric mediators showed that these are not suited for this transformation, underscoring the need for the *in situ* oxidation of the iodide which, according to previous observations under similar reaction conditions,[6,10] strongly supports that the corresponding ammonium hypoiodite is the catalytically relevant species.
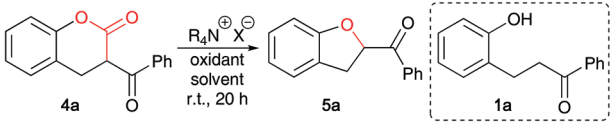
Alternative oxidants were not suited (entries 8 and 9), while a solvent screening showed that CH₂Cl₂ allows for cleaner and higher yielding reactions compared to other classical organic solvents (compare entries 10–12). The effect of catalyst loading

and H₂O₂ excess was tested in CH₂Cl₂ as well, but again lower amounts result in lower yields (entries 13 and 14).

Mechanistically, the whole process is supposed to proceed *via* lactone opening-decarboxylation first (most likely facilitated by the *in situ* formed reasonably basic hypoiodite species[14]), followed by the oxidative cycloetherification of the intermediate phenol derivative **1a** (Scheme 2A). Although it was not possible to detect this intermediate in our reaction mixture by ¹H NMR or HRMS studies, it was found that lactone **4a** undergoes a Bu₄NI-mediated decarboxylation under basic conditions in the absence of oxidant (Table 1, entry 15). Compound **1a** then undergoes the oxidative cyclization towards **5a** when submitted to our standard reaction conditions in analogy to Ishihara's work.[6a] Noteworthy, this stepwise process was found to be slower than the standard cascade approach, requiring around 2 days for the cyclization of **1a–5a** to complete, suggesting that in our case the *in situ* formed enolate of **1a** directly undergoes the oxidative cycloetherification (most likely *via* intermediates **Int-I** or **Int-II**). Control experiments carried out in the presence of TEMPO or BHT proceeded readily with the same conversion and yield as in their absence, thus making a radical mechanism unlikely.
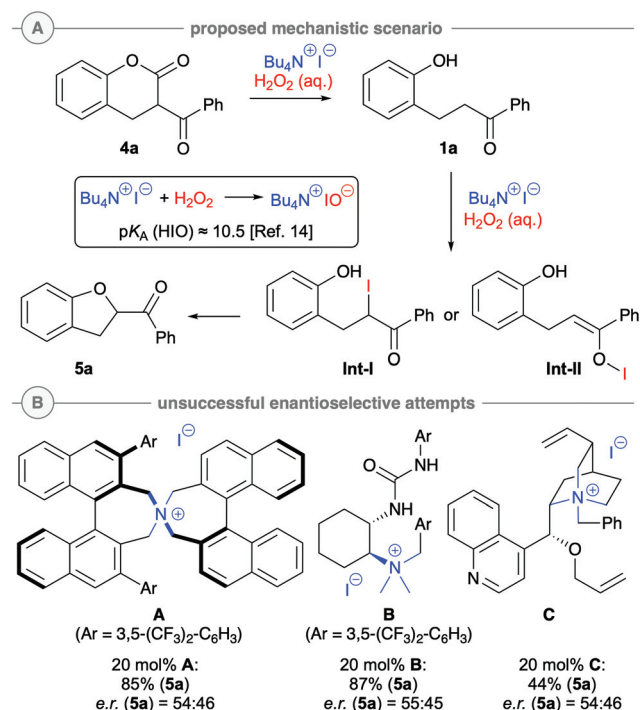
Attempts to render the whole process enantioselective by utilizing chiral ammonium iodide catalysts were unfortunately less satisfactory, as no noteworthy selectivities could be achieved by screening a variety of different catalysts under the established racemic conditions as well as using other solvents (er <55 : 45, Scheme 2B). In addition, we also tried to utilize (chiral) aryliodides as catalysts under oxidative conditions,[1,3,4]

Table 1 Optimization of the reaction conditions for the synthesis of **5a**[a]

Entry	Cat. (mol%)	Oxidant (eq.)	Solvent	**5a**[b] [%]
1	Bu₄NI (10%)	H₂O₂ (3×)	Toluene	51
2	Bu₄NI (30%)	H₂O₂ (3×)	Toluene	63
3	Bu₄NI (30%)	H₂O₂ (1×)	Toluene	15
4	Bu₄NBr (30%)	H₂O₂ (3×)	Toluene	Traces
5	Bu₄NCl (30%)	H₂O₂ (3×)	Toluene	—
6	Bu₄NI₃ (100%)	—	Toluene	—
7	Bu₄NIO₃ (100%)	—	Toluene	—
8	Bu₄NI (30%)	Oxone (3×)	Toluene	Traces
9	Bu₄NI (30%)	*t*-BuOOH (3×)	Toluene	Traces
10	Bu₄NI (30%)	H₂O₂ (3×)	EtOAc	73
11	Bu₄NI (30%)	H₂O₂ (3×)	CH₃CN	65
12	Bu₄NI (30%)	H₂O₂ (3×)	CH₂Cl₂	89 (84)[c]
13	Bu₄NI (20%)	H₂O₂ (3×)	CH₂Cl₂	56
14	Bu₄NI (30%)	H₂O₂ (2×)	CH₃CN	59
15	Bu₄NI (30%)	NaOH (3×)	CH₂Cl₂	**1a**

[a] Reactions were run for 20 h at r.t. using 0.1 mmol **4a** in the presence of the given catalyst in the indicated solvent (*c* = 0.1 M with respect to **4a**). [b] Isolated yields. [c] 1 mmol scale.


Scheme 2 Mechanistic proposal (A) and exemplified unsuccessful asymmetric attempts (B).

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but no product formation could be observed at all, thus substantiating the need for the quaternary ammonium hypoiodite catalyst system herein.

Based on these results, we next investigated the racemic application scope of this protocol by subjecting a variety of differently substituted lactones **4** to the optimized reaction conditions (Scheme 3). In general, the methodology was found to be pretty robust, tolerating different aryl groups and aromatic R^2 substituents (giving products **5a–5n**). Notably, naphthyl-based dihydrobenzofurans like compounds **5k–n** recently showed promising anti-cancer properties,[15] thus underscoring the value of new methods for their syntheses. In addition, it was possible to utilize substrates with a benzylic R^1 substituents as well, resulting in the formation of the products **5o–q** as mixtures of diastereomers. Interestingly, while the *trans* isomers were preferred for the Me-containing **5o** and the TMSCH$_2$-substituted **5q**, the *cis* isomer was slightly favoured for the iPr-based **5p** (assignment of the relative configuration was carried out by comparison with reported examples,[12a] analysis of the ^3J coupling constants[13] and comparison of the experimental values with calculated results of DFT-optimized structures).
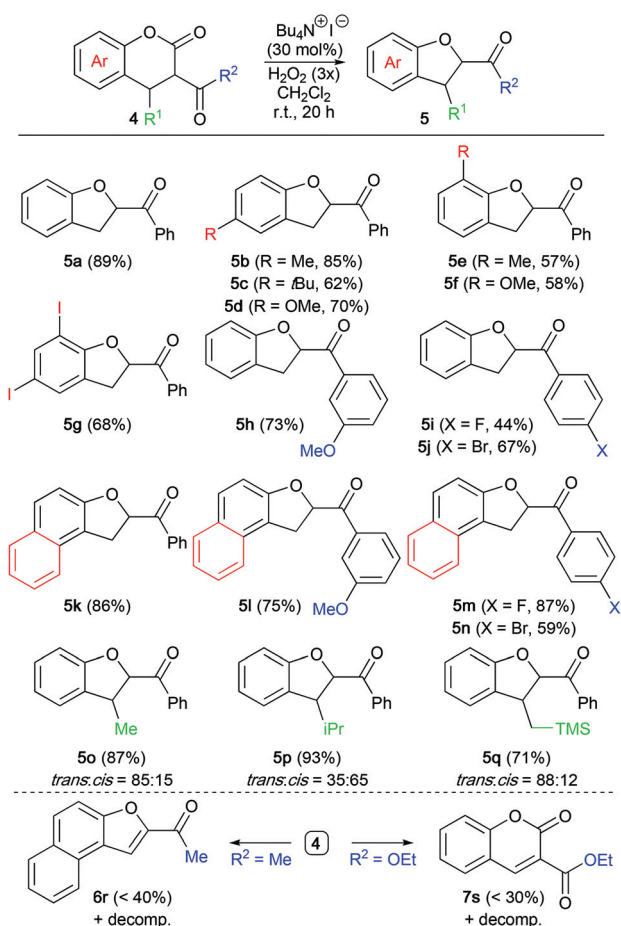
Unfortunately, the method came to its limits when using methyl ketone-based starting materials or ester-based ones. While the presence of an ester R^2-group did prevent the decarboxylative cycloetherification and rather led to α,β-unsaturated products (as exemplified for compound **7s**), methyl ketones reacted directly to the corresponding benzofurans, as outlined for derivative **6r** (it should be emphasized that both reactions gave large amounts of unidentified decomposition products too). Formation of compound **7s** can be rationalized by an oxidative α-iodination of starting material **4s** first, followed by elimination. Product **6r** on the other hand is most likely formed *via* immediate overoxidation (α-iodination–elimination sequence) of the initially formed dihydrobenzofuran **5r**. Unfortunately, it was not possible to achieve higher yields hereby when testing different reaction conditions however. Interestingly, small levels (<15%) of this kind of overoxidation were also observed for some other derivatives containing an aromatic R^2 group (*i.e.* for compounds **5c**, **5h**, and **5l**),[13] but in neither case was this the dominant process as found for the methyl ketones.

In conclusion, we have developed a protocol for the synthesis of dihydrobenzofurans **5** starting from lactones **4** relying on the catalytic use of quaternary ammonium iodides under oxidative conditions. This approach most presumably proceeds *via in situ* ammonium hypoiodite generation and this latter species facilitates the overall decarboxylative oxidative cycloetherification sequence under operationally simple conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Scheme 3 Application scope of the racemic oxidative decarboxylative cycloetherification.

Notes and references

1 (a) *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, ed. V. V. Zhdankin, John Wiley & Sons, New York, 2014; (b) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299–5358; (c) *Iodine Catalysis in Organic Synthesis*, ed. K. Ishihara and K. Muniz, Wiley-VCH, 2022.

2 (a) M. Uyanik and K. Ishihara, *ChemCatChem*, 2012, **4**, 177–185; (b) X.-F. Wu, J.-L. Gong and X. Qi, *Org. Biomol. Chem.*, 2014, **12**, 5807–5817.

3 (a) A. Claraz and G. Masson, *Org. Biomol. Chem.*, 2018, **16**, 5386–5402; (b) C. Mairhofer, L. Stockhammer and M. Waser, *ARKIVOC*, 2021, **vii**, 112–127.

4 (a) F. V. Singh and T. Wirth, *Chem. – Asian J.*, 2014, **9**, 950–971; (b) M. Uyanik, in *Iodine Catalysis in Organic Synthesis*,

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Org. Biomol. Chem., 2022, **20**, 3273–3276 | **3275**

ed. K. Ishihara and K. Muniz, Wiley-VCH, 2022, pp. 275–298.

5 P. Ghosh, B. Ganguly and S. Das, *Org. Biomol. Chem.*, 2021, **19**, 2146–2167.

6 (*a*) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376–1379; (*b*) M. Uyanik, H. Hayashi and K. Ishihara, *Science*, 2014, **345**, 291–294.

7 (*a*) M. Uyanik, D. Suzuki, M. Watanabe, H. Tanaka, K. Furukawa and K. Ishihara, *Chem. Lett.*, 2015, **44**, 387–389; (*b*) M. Uyanik, H. Hayashi, H. Iwata and K. Ishihara, *Chem. Lett.*, 2016, **45**, 353–355; (*c*) M. Uyanik, T. Kato, N. Sahara, O. Katade and K. Ishihara, *ACS Catal.*, 2019, **9**, 11619–11626.

8 (*a*) M. Uyanik, K. Nishioka, R. Kondo and K. Ishihara, *Nat. Chem.*, 2020, **12**, 353–362; (*b*) M. Uyanik, N. Sahara, M. Tsukahara, Y. Hattori and K. Ishihara, *Angew. Chem., Int. Ed.*, 2020, **59**, 17110–17117; (*c*) M. Uyanik, D. Nagata and K. Ishihara, *Chem. Commun.*, 2021, **57**, 11625–11628.

9 (*a*) S. Guo, J.-T. Yu, Q. Dai, H. Yang and J. Cheng, *Chem. Commun.*, 2014, **50**, 6240–6242; (*b*) K. Yasui, T. Kato, K. Kojima and K. Nagasawa, *Chem. Commun.*, 2015, **51**, 2290–2293; (*c*) W.-C. Gao, F. Hu, J. Tian, X. Li, W.-L. Wei and H.-H. Chang, *Chem. Commun.*, 2016, **52**, 13097–13100;

(*d*) J.-Q. Han, H.-H. Zhang, P.-F. Xu and Y.-C. Luo, *Org. Lett.*, 2016, **18**, 5212–5215; (*e*) D. Wang, X. Lu, S. Sun, H. Yu, H. Su, Y. Wu and F. Zhong, *Eur. J. Org. Chem.*, 2019, 6028–6033; (*f*) D. Wang, W. Zhang, X. Lu, H. Zhou and F. Zhong, *Org. Lett.*, 2022, **24**, 842–847.

10 C. Mairhofer, J. Novacek and M. Waser, *Org. Lett.*, 2020, **22**, 6138–6142.

11 (*a*) S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4312–4348; (*b*) S. Kaneko, Y. Kumatabara and S. Shirakawa, *Org. Biomol. Chem.*, 2016, **14**, 5367–5376; (*c*) D. Qia and J. Sun, *Chem. – Eur. J.*, 2019, **25**, 3740–3751.

12 (*a*) N. Meisinger, L. Roiser, U. Monkowius, M. Himmelsbach, R. Robiette and M. Waser, *Chem. – Eur. J.*, 2017, **23**, 5137–5142; (*b*) K. Zielke and M. Waser, *Org. Lett.*, 2018, **20**, 768–771; (*c*) K. Zielke, O. Kovac, M. Winter, J. Pospisil and M. Waser, *Chem. – Eur. J.*, 2019, **25**, 8163–8168.

13 Details can be found in the ESI.†

14 J. Paquette and B. L. Ford, *Can. J. Chem.*, 1985, **63**, 2444–2448.

15 K. Islam, K. Pal, U. Debnath, R. S. Basha, A. T. Khan, K. Jana and A. K. Misra, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127476.

3276 | *Org. Biomol. Chem.*, 2022, **20**, 3273–3276

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