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Oxidative decarboxylative ammonium hypoioditecatalysed 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 (I₃, IO_n^{-}) can be achieved, amongst which ammonium hypoiodite derivatives R₄N⁺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 Maruokatype 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 R¹ 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 H_2O_2 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 species¹⁴), 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	s for the synth	esis of 5a ª
	$\begin{array}{c} \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$		Ia	Ph
Entry	Cat. (mol%)	Oxidant (eq.)	Solvent	$5a^{b}[\%]$
1	Bu ₄ NI (10%)	$H_2O_2(3\times)$	Toluene	51
2	Bu ₄ NI (30%)	$H_2O_2(3\times)$	Toluene	63
3	Bu ₄ NI (30%)	$H_2O_2(1\times)$	Toluene	15
4	B11 NBr (200%)	HO(2x)	Toluene	Traces

-		2-2(-)		
5	Bu_4NCl (30%)	$H_2O_2(3\times)$	Toluene	
5	Bu_4NI_3 (100%)	_	Toluene	
7	Bu_4NIO_3 (100%)		Toluene	_
3	$Bu_4NI(30\%)$	Oxone (3×)	Toluene	Traces
)	$Bu_4NI(30\%)$	t-BuOOH (3×)	Toluene	Traces
10	$Bu_4NI(30\%)$	$H_2O_2(3\times)$	EtOAc	73
1	$Bu_4NI(30\%)$	$H_2O_2(3\times)$	CH ₃ CN	65
12	$Bu_4NI(30\%)$	$H_2O_2(3\times)$	CH_2Cl_2	89 (84)
13	$Bu_4NI(20\%)$	$H_2O_2(3\times)$	CH_2Cl_2	56
14	$Bu_4NI(30\%)$	$H_2O_2(2\times)$	CH ₃ CN	59
15	$Bu_4NI(30\%)$	NaOH (3×)	CH_2Cl_2	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).

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 R¹ substituents as well, resulting in the formation of the products 50-q as mixtures of diastereomers. Interestingly, while the trans isomers were preferred for the Me-containing 50 and the TMSCH₂-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 constants¹³ and comparison of the experimental values with calculated results of DFT-optimized structures).



Scheme 3 Application scope of the racemic oxidative decarboxylative cycloetherification.

Unfortunately, the method came to its limits when using methyl ketone-based starting materials or ester-based ones. While the presence of an ester R²-group did prevent the decarboxylative cycloetherification and rather led to α,β -unsatured 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 \mathbb{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.

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