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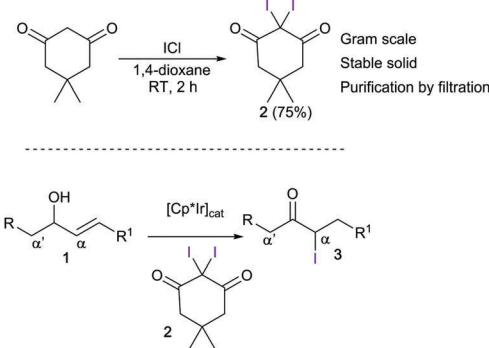
2,2-Diiododimedone is reported as a new electrophilic iodinating agent that selectively iodinates electron-rich aromatics. In contrast to other common electrophilic iodinating reagents, its mild nature allows it to be used for the selective synthesis of α -iodinated carbonyl compounds from allylic alcohols through a 1,3-hydrogen shift/iodination process catalyzed by iridium(III) complexes.

Halogenated organic compounds are ubiquitous, not only as natural products,¹ but also as synthetic compounds, and they have applications in medicinal chemistry,² agrochemistry,³ and materials science.⁴ The halogen functional group is very versatile. It can participate in many synthetic transformations, including nucleophilic substitutions, eliminations, dehydrohalogenations, and oxidative additions to metal centers. The nature of the halogen gives each carbon–halogen bond unique properties,⁵ resulting in numerous applications in synthetic organic chemistry.

Significant progress has been made in the development of synthetic methods for the construction of C–F bonds, *via* both electrophilic and nucleophilic approaches.⁶ There also exist many synthetic methods for the nucleophilic and electrophilic chlorination⁷ and bromination⁸ of organic molecules. When it comes to electrophilic methods for the construction of C–I bonds, reagents such as I₂, NIS (*N*-iodosuccinimide), IPy₂BF₄ (Barluenga's reagent), and ICl have been widely used in organic synthesis.⁹ Also, methods based on the conversion of iodide into the corresponding iodonium species through oxidation have also been reported.¹⁰ These methods have some drawbacks, however, such as the high reactivity of the electrophilic iodinating agents, or the need for strong oxidizing agents, which result in low functional-group tolerance and low chemo- or regioselectivity. Thus, the development of mild and selective electrophilic

iodination methods remains a challenging and desirable goal for synthetic chemists.

We have previously reported the use of iridium catalysts for the conversion of allylic alcohols (**1**) into α -functionalized carbonyl compounds.^{11,7c,8c,12} Carbon and halogen (*i.e.*, F, Cl, and Br) functional groups could be introduced through a process involving a 1,3-hydrogen shift mediated by the metal complex. This process allows the selective formation of either the α or α' constitutional isomer, as the new bond is constructed exclusively at the carbon that was originally part of the olefin. Attempts to introduce an iodide failed in our hands, mainly due to the high reactivity of the available electrophilic iodinating agents, but also due to the instability of the starting allylic alcohols and/or the final iodoketones under the reaction conditions. In this communication, we report the development of a new mild iodinating agent (Scheme 1, top) and its application in electrophilic iodination of aromatic compounds, and also in the synthesis of α -iodoketones (**3**) from allylic alcohols mediated by iridium catalysts (Scheme 1, bottom). This methodology allows for the first time the one-step synthesis of α -iodoketones as single constitutional isomers from allylic alcohols in a one-step procedure. The utility of α -iodoketones for the preparation of valuable building blocks is also presented.



Scheme 1 Synthesis of 2,2-diiododimedone (**2**, top) and of α -iodocarbonyl compounds from allylic alcohols.

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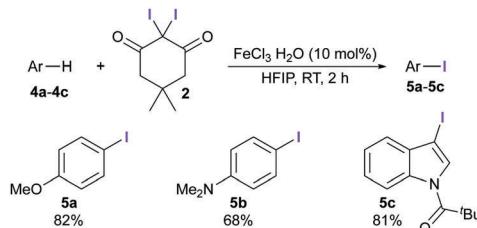
† Electronic supplementary information (ESI) available: Detailed synthetic procedures, characterization, NMR spectra, optimization tables and deuterium labelling studies. See DOI: 10.1039/c7cc04823h

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The synthesis of the new iodinating reagent, 2,2-diiododimedone (2), was easily accomplished by the treatment of dimedone with iodine monochloride in 1,4-dioxane at room temperature. The synthesis of 2 can be carried out on a gram scale, and purification by simple filtration gives the product in excellent yield. We initially tested 2 as an iodinating agent for aromatic compounds (Scheme 2). In optimization studies, the best results were obtained using a catalytic amount of FeCl_3 , and hexafluoroisopropanol (HFIP) as the solvent. The need to use these conditions reflects the mildness of 2, which is important for increasing the functional group tolerance in electrophilic halogenation reactions. After a short optimization (see ESI†), we found that anisole (4a) could be iodinated under an air atmosphere in just 2 h. Two other substrates were also iodinated using these reaction conditions; both *N,N*-dimethylaniline (4b) and *N*-pivaloyl indole (4c) were converted into the corresponding iodinated analogues (5b and 5c) in very good yields after short reaction times and with excellent regioselectivity.

Next, we evaluated the performance of 2 in the iridium-catalyzed isomerization/α-iodination of allylic alcohols. For a successful outcome, the reaction must take place under mild conditions, and the starting alcohols (1) and final products (3) should not undergo undesired iodination. Oct-1-en-3-ol (1a) was chosen as a model substrate for the optimization studies, and several Ir(III) catalysts and solvents were evaluated (Table 1). When $[\text{Cp}^*\text{IrCl}_2]_2$ (I, 2 mol% [Ir]) was used as the catalyst in a mixture of acetone and H_2O (1:1), full conversion was observed, but only 34% of the desired product 3a was formed, together with 64% of α,β-unsaturated ketone 6a (entry 1). This solvent mixture gave, on the contrary, excellent results in the bromination of allylic alcohols.^{8c} The use of $\text{THF}/\text{H}_2\text{O}$ (1:1) resulted in a clear decrease in the formation of 6a (entry 2). This effect was even clearer when THF was replaced by 2-methyltetrahydrofuran (2-MeTHF). In this case, the desired α-iodinated compound (3a) was obtained in 85% yield and only 11% of 6a was formed (entry 3). The amount of 6a could be decreased further by using $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3]\text{SO}_4$ (II) or $[(\text{Cp}^*\text{Ir})_2(\text{OH})_3]\text{OH} \cdot 11\text{H}_2\text{O}$ (III) as the catalyst (entries 4 and 5). When the proportion of H_2O in the solvent mixture was increased (*i.e.*, 1:2), higher amounts of the undesired 6a were formed (entries 6 and 7); when the proportion of 2-MeTHF was increased, the yield of 6a dropped to just 5–6% (entries 8 and 9), while a very good yield for 3a was maintained. Increasing the proportion of 2-MeTHF further did not prevent the formation of 6a, and also compromised the conversion (see the ESI† for a full description of solvent effects).



Scheme 2 Iodination of electron-rich aromatics using 2.

Table 1 Optimization^a

Entry	Catalyst	Solvent (v/v)	Conv. ^b [%]	3a/6a ^{b,c} [%]		
				[Cp*IrCl ₂] ₂ I	[Cp*Ir(H ₂ O) ₃]SO ₄ II	[(Cp*Ir) ₂ (OH) ₃]OH · 11H ₂ O III
1	I	Acetone/ H_2O (1:1)	>99	36/64		
2	I	THF/ H_2O (1:1)	86	58/28		
3	I	2-MeTHF/ H_2O (1:1)	96	85/11		
4	II	2-MeTHF/ H_2O (1:1)	99	93/6		
5	III	2-MeTHF/ H_2O (1:1)	>99	92/8		
6	II	2-MeTHF/ H_2O (1:2)	>99	91/9		
7	III	2-MeTHF/ H_2O (1:2)	>99	90/10		
8	II	2-MeTHF/ H_2O (2:1)	98	93/5		
9	III	2-MeTHF/ H_2O (2:1)	>99	94/6		
10 ^d	II	2-MeTHF/ H_2O (2:1)	86	79/7		
11 ^d	III	2-MeTHF/ H_2O (2:1)	92	88/4		

^a Unless otherwise noted, 1a (0.5 mmol, 0.1 M) and 2 mol% [Ir] were used. ^b Determined by ¹H NMR spectroscopy. ^c Octan-3-one was not formed. ^d 1 mol% [Ir].

When the catalyst loading was decreased to 1 mol% [Ir], catalyst III was better than II (entries 10 and 11). When 0.6 and 0.2 equiv. of 2 were used, yields of 70 and 27%, respectively, were observed (see ESI†). This result suggests that more than one iodo unit can be donated by the reagent. All reactions were carried out under an atmosphere of air.

When compared to other electrophilic iodinating reagents, the superiority of 2 was clearly seen (Table 2). None of the other reagents tested were able to give good yields of 3a, mainly due to the decomposition of the starting allylic alcohol 1a (entries 1–5). This is not surprising, since it is well known that double bonds promptly react with these reagents to give cyclic iodonium ions. This undesired reaction was not observed when 2,2-diiododimedone

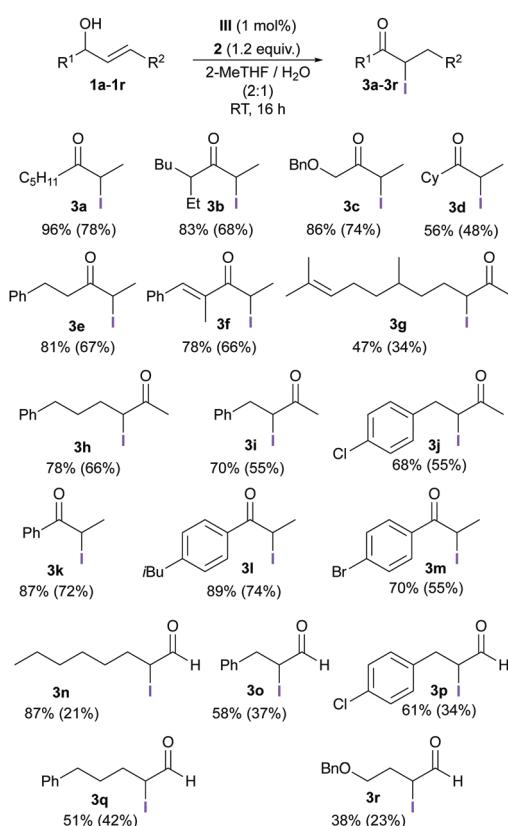
Table 2 Evaluation of a variety of iodinating agents^a

Entry	Reagent	Conv. ^b [%]	3a/6a ^b [%]	
			[Cp*Ir] _{cat} (III, 1 mol%) Iodinating agent (1.2 equiv.)	Solvent RT, 16 h
1	2	>99	94/6	
2	I_2	66	—/3 ^c	
3	ICl	66	—/1 ^c	
4	NIS	>99	17/—	
5	IPy_2BF_4	>99	—/—	
6	—	<5	—	
7	2 ^d	4	—	
8	I_2^d	25	— ^e	
9	ICl ^d	95	— ^e	
10	NIS ^d	90	— ^e	
11	$\text{IPy}_2\text{BF}_4^d$	76	— ^e	

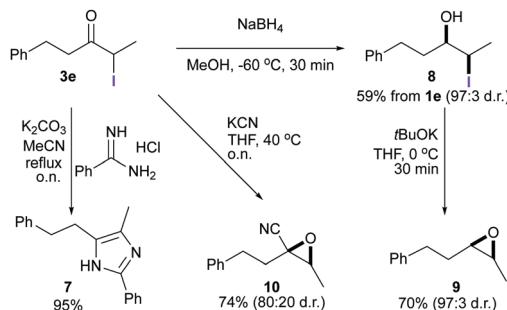
^a Unless otherwise noted, 1a (0.5 mmol, 0.1 M). ^b Determined by ¹H NMR spectroscopy. ^c 28% (entry 2) and 21% (entry 3) of octan-3-one were formed. ^d Without [Ir] catalyst. ^e A mixture of unknown by-products was observed.

(2) was used. A series of control experiments was also carried out (Table 2, entries 6–11). Catalyst **III** alone was not able to react with the allylic alcohol in the absence of **2** (entry 6). We recently reported that the presence of a halogen ligand on Ir is important for the activity of $[\text{Cp}^*\text{Ir}]$ complexes of this type, and described the *in situ* formation of such an Ir–halogen bond through the reaction of the Ir precatalyst with the halogenating agent.¹³ In another control experiment, we observed that **2** does not react with allylic alcohol **1a** in the absence of the iridium catalyst after 16 h (entry 7). It can therefore be concluded that the mildness of the iodinating agent **2** is key to the success of this tandem isomerization/halogenation reaction. Mechanistic investigations were carried out with deuterium-labelled alcohols, and the results suggest that an intramolecular 1,3-H shift is operating under these reaction conditions (see ESI†).

Having established these optimized reaction conditions, we went on to study the scope of the reaction (Table 3). Alcohols **1a–1f** and **1k–1m** bearing a terminal double bond gave the corresponding α -iodocarbonyl compounds (**3a–3f** and **3k–3m**) in high yields within 16 h. Allylic alcohols with internal double bonds (**1g–1j**) were also converted into the corresponding α -iodinated products in good yields. Additional double bonds in the molecule were unaffected (**1f** and **1g**); only the allylic alcohol functionality reacted. The reaction is not restricted to

Table 3 Substrate scope^a

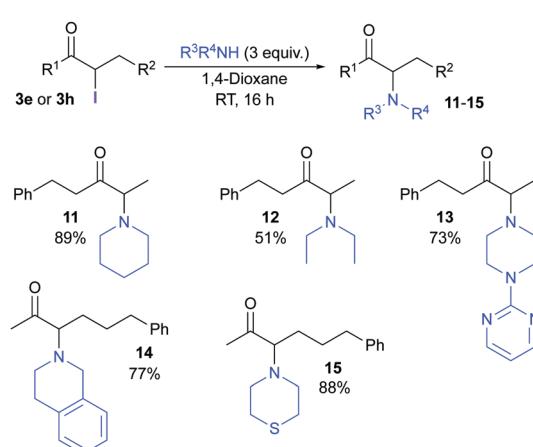
^a Reactions carried out on a 1 mmol scale (0.1 M). Yield determined by ^1H NMR spectroscopy. Isolated yields in parentheses.

Scheme 3 α -Iodoketones as versatile synthetic intermediates.

secondary alcohols; primary alcohols gave the corresponding α -iodoaldehydes (**3n–3r**) in moderate to good yields. The stability of the products during the purification process accounts for the difference between the yields estimated against an internal standard and the isolated yields.

The utility of α -iodoketones as versatile intermediates for organic synthesis was demonstrated in a series of transformations (Schemes 3 and 4). First, the synthesis of imidazole **7** was easily accomplished by allowing an amidine to react with α -iodoketone **3e**. In a one-pot procedure starting from **1e**, iodoalhydrin **8** was synthesized in 59% yield with excellent diastereoselectivity (93:7). Subsequent basic treatment gave the corresponding epoxide **9** with excellent diastereoselectivity. α -Cyanoepoxide **10** was also prepared in good yield and with a good diastereomeric ratio in one step by the reaction of **3e** with KCN.

The synthetic utility of α -iodocarbonyl compounds was also demonstrated *via* the preparation of valuable α -aminoketones. This structural motif is found in many compounds with important biological activities.¹⁴ Although there are several procedures for the synthesis of compounds containing this motif, their regioselective preparation when two enolizable positions are present remains a challenge.^{14b–d} We found that secondary amines react with α -iodocarbonyl derivatives – prepared from allylic alcohols as described in this communication – to give α -amino ketones as single constitutional isomers (Scheme 4).

Scheme 4 Regioselective synthesis of α -amino ketones.

In conclusion, we present a new mild and selective electrophilic iodinating reagent, 2,2-diiododimedone (2). Using this reagent, we have been able to carry out the first selective synthesis of α -iodocarbonyl compounds as single constitutional isomers. The method relies on an iridium-catalyzed 1,3-hydrogen shift mediated by iridium(III) complexes. The utility of α -iodocarbonyl compounds has been demonstrated by their conversion into other important organic structures for which selective synthetic procedures have not previously been available.

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Conflicts of interest

There are no conflicts to declare.

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