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Base- and Additive-Free Ir-Catalyzed *ortho*-lodination of Benzoic Acids: Scope and Mechanistic Investigations

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ABSTRACT: A protocol for the C–H activation/iodination of benzoic acids catalyzed by a simple iridium complex has been developed. The method described in this paper allows the *ortho*-selective iodination of a variety of benzoic acids under extraordinarily mild conditions in the absence of any additive or base in 1,1,1,3,3,3-hexafluoroisopropanol as the solvent. The iridium catalyst used tolerates air and moisture, and selectively gives *ortho*-iodobenzoic acids with high conversions. Mechanistic investigations revealed that an Ir(III)/Ir(V) catalytic cycle operates, and that the unique properties of HFIP enables the C–H iodination using the carboxylic moiety as a directing group.

KEYWORDS: C-H iodination, benzoic acids, iridium catalysis, 1,1,1,3,3,3-hexafluoroisopropanol, hydrogen bonding.

1. INTRODUCTION

Transition-metal-directed activation of inert C–H bonds is one of the most efficient ways to introduce functional groups into organic molecules. The combined use of molecules bearing directing groups with the aid of transition-metal catalysts enables the regioselective activation and functionalization of particular C–H bonds.¹

Compounds containing aromatic halides are important building blocks that are ubiquitous in synthetic organic chemistry laboratories. They play pivotal roles in drug and natural-product syntheses.² Furthermore, aromatic bromides and iodides have been extensively used in cross-coupling³ and in Grignard reactions.⁴ The functionalization of aromatic compounds with halides through the direct activation of C-H bonds is a straightforward way to obtain halogenated aromatics. The first examples have been reported only in the last decade, and were limited to the use of strong, nitrogencontaining directing groups, using palladium catalysis.⁵ We have also recently reported a heterogeneous Pd catalyst that halogenates nitrogen-functionalized aromatics.⁶ More recently, different arenes bearing several directing groups, including amides, ketones, and even carbamates could be halogenated in the ortho position by transition metal catalysts.^{7,8,9} In this context, Nicholls and coworkers^{9h} reported the only example for this transformation employing an Ir catalyst. They described the ortho-halogenation of acetanilides employing [Cp*IrCl₂]₂. The use of catalytic amounts of Boc-L-Phe and AgNTf2 were necessary to obtain high yields and good regiocontrol.

Carboxylic acids are ubiquitous in natural products.¹⁰ However, their use as *ortho*-directing groups in reactions involving the activation of C–H bonds has been challenging in terms of yields and selectivity. This is partly due to that in the absence of catalyst, the carboxylic acid moiety is a *meta*-directing group. This is not the case with for example anilines and derivatives,^{9h} which direct the functionalization to the *ortho* and *para* positions even in the absence of



Scheme 1. C-H iodination of benzoic acids.

catalysts. During the last few years, however, this field has experienced significant development,¹¹ and a variety of methods to construct C–C and C–N bonds have been described using Pd,¹² Ru¹³ and Rh.¹⁴ With regard to the use of iridium catalysts, Satoh and Miura,¹⁵ and Ison¹⁶ reported the oxidative coupling reaction of benzoic acids with alkynes, yielding naphthalenes and isocoumarines. Very recently, Zeng's group reported the *o*-alkynylation of carboxylic acids using excess of KHCO₃.¹⁷ Gooßen has described the *o*-arylation of carboxylic acids with arenediazonium salts in the presence of Ag₂CO₃ and Li₂CO₃.¹⁸ Iridium-catalyzed *ortho*-C–H amidation of benzoic acids with sulfonyl azides using AgNTf₂, AcOH and Li₂CO₃ as additives was described by Cui and co-workers.¹⁹

The introduction of halides into benzoic acids through C-H activation has been, however, quite limited, despite the potential utility of such substrates.¹¹ There is only one report, by Yu and coworkers, that describes the ortho-iodination of carboxylic acids,²⁰ where Pd(OAc)₂ is used in the presence of superstoichiometric amounts of IOAc. This method afforded good yields at 100 °C in 36 h. The direct C-H iodination of benzoic acids under milder reaction conditions would allow the introduction of iodide at a late stage, and a C-H iodination protocol avoiding the use of additives (i.e., bases, silver salts, or strong oxidants) would significantly increase the functional-group tolerance as well as the atom economy.

Our group has gained extensive knowledge about the selective transition-metal-catalyzed halogenation of molecules.²¹ We have reported 1,3-hydrogen shift / halogenation protocols for aliphatic and aromatic allylic alcohols under mild conditions using iridium catalysis. In this paper, we report a mild, efficient, and extraordinarily simple method for the selective ortho C-H iodination of benzoic acids catalyzed by a P/N-ligandless Ir(III) catalyst (Scheme 1). Experimental and theoretical investigations elucidating the mechanism and the unique role of the solvent are also presented.

2. RESULTS AND DISCUSSION

We started using 2-methylbenzoic acid (1a) as the model substrate with NIS (N-iodosuccinimide) as the halogenating agent, and investigated the influence of a number of parameters (Table 1 and S1). Due to their excellent performance in halogenation reactions under both air and water,²¹ and inspired by the reaction conditions reported by Gooßen¹⁸ for C-H arylations, we investigated complexes of the general structure [Cp*Ir(III)]. Glorius has also reported excellent results using related [Cp*Rh(III)X2] complexes in the C-H halogenation of other aromatic compounds.8

When **1a** was treated with 3 equiv. of NIS and [Cp*IrCl₂]₂ in the presence of catalytic amounts of AgBF₄ and NaOAc (Table 1), in acetone at 60 °C, a 25% yield of 2b was obtained (entry 1). Other solvents were tested under otherwise identical conditions (Table S1), but the best results were obtained in HFIP (1,1,1,3,3,3-hexafluoroisopropanol), which gave 2a in 86% yield (entry 2). With chloride-free ($[Cp*Ir(H_2O)_3]SO_4$) **II**, easily prepared from **I**,²² the yield increased to 90% (entry 3). The temperature could be lowered to 40 °C without compromising the yield (entry 4). In the absence of additives, the yield did not decrease, giving 2a in 88% yield (entry 5). Furthermore, with only 1.5 equiv. of NIS, 2a was formed in nearly quantitative yield (entry 6). Intrigued by these excellent results without additives, we wondered whether the solvent had a significant impact on the reaction. In acetone, 1,2-dichloroethane (DCE), or THF no product was obtained at 40 °C (entries 7-9). Interestingly, PrOH did not yield any product. In contrast, 2,2,2trifluoroethanol (TFE), gave a 73% yield (entry 11). Thus, protic solvents with low pK_a values such as HFIP ($pK_a = 9.3$) or TFE ($pK_a = 12.4$) give the best results. In more acidic

solvents, such as CF₃CO₂H (TFA) ($pK_a = 0.2$) the activity was compromised (entry 12). Under the optimal conditions, we evaluated again the catalytic activity of chloride complex I, which afforded 2a in only 40% yield after 16 h (entry 13). Upon increasing the temperature to 70 °C, 2a was obtained in 77% yield after 48 h, together with 15% of starting material, the reminder being unidentified by-products (entry 14). A control experiment in the absence of catalyst resulted in iodination of the *meta* position in 56% yield (entry 15). This background meta-iodination is completely suppressed under the catalytic conditions reported here. All reactions were carried out under an atmosphere of air.

Table 1. Screening of the reaction conditions.^a

CH ₃ O H H	Ir (3 mol Additive NIS Solvent, T,	%) CH 25 16 h	H ₃ O OH	[Cp*lrCl₂]₂ I	[Cp*lr(H ₂ O) ₃ II	3]SO4
Entry	Solvent	T (°C)	Cat	Additives	NIS (equiv.)	Yield $(\%)^b$
1	Acetone	60	Ι	AgBF ₄ / NaOAc	3	25
2	HFIP	60	I	AgBF ₄ / NaOAc	3	86
3	HFIP	60	п	AgBF ₄ / NaOAc	3	90
4	HFIP	40	п	AgBF ₄ / NaOAc	3	86
5	HFIP	40	Π	-	3	88
6	HFIP	40	Π	-	1.5	98 ^c
7	Acetone	40	п	-	1.5	5

6	HFIP	40	ш	-	1.5	98.
7	Acetone	40	п	-	1.5	5
8	DCE^d	40	п	-	1.5	0
9	THF	40	Π	-	1.5	0
10	ⁱ PrOH	40	п	-	1.5	0
11	TFE^{e}	40	п	-	1.5	73
12	TFA^{f}	40	п	-	1.5	0
13	HFIP	40	Ι	-	1.5	40
14	HFIP	70	Ι	-	1.5	77 ^g
15	HFIP	40	-	-	1.5	0^{h}

"Unless otherwise noted, all experiments were carried out under air atmosphere on 0.15 mmol scale of 1a and 0.1 M. AgBF₄ (20 mol %), NaOAc (30 mol %) for 16 h. ^bDetermined by ¹H NMR spectroscopy against an internal standard (1,2,4,5-tetrachloro-3-nitrobenzene). ^cIsolated yield. ^{*d*}DCE = 1,2-dichloroethane. ^{*e*}TFE = 2,2,2-trifluoroethanol. ^fTFA = trifluoroacetic acid. ^gYield of **2a** after 48 h. The reminder being 15% of starting material and 8% of unidentified by-products ^hIodination in meta position in 56% yield after 18 h.

The compatibility of the reaction conditions with different functional groups was preliminary evaluated by performing a robustness-screening test²³ (Scheme 2). Thus, the iridiumcatalyzed C-H iodination reaction in the presence of a variety of functionalized molecules. Under the optimal conditions (Table 1, entry 6), amines, amides, ethers, esters, alcohols and halogenated compounds were well tolerated, and 2a was obtained in good yield (Scheme 2 and Table S2). On the other hand, the reaction is non-compatible with double or triple bonds, nor with carbonyl functional groups (see SI for further details).

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Based on the results from the robutness-screening test, the scope of the reaction was investigated. Iodinated products

from o-substituted benzoic acids (1a-1p) were obtained in very high yields (Scheme 3). Among these, substrates bearing halogens substituents (1b-1d) gave yields from 70 to 98%. Lower yields were obtained for the more electronwithdrawing CF₃ and NO₂ (1e-1f).[¶] Alcohols, ethers, esters, carboxylic acids,§ amines and amides are well tolerated in agreement with the robustness test, and 2g-2p were obtained in high yields showing the broad functional group tolerance of this methodology. Selectively monoiodinated products were obtained with *meta*-substituted 1q-1t. Highly substituted benzoic acids 1u-1ab were also iodinated. Full control over the regioselectivity was also obtained in substrates with two ortho C-H positions (2q-v).[¥] Benzoic acid itself gave a mixture of mono- and diiodinated products 2ac and 3ac, respectively. By increasing the catalyst loading and the number of equivalents of NIS, 3ac was obtained as the major product. Under these conditions, 1q gave diiodinated 3q, and 1ad and 1ae, the latter with two acid groups, were diiodinat-



Scheme 3. Scope of the reaction. Isolated yields (yield by ¹H NMR spectroscopy in parentheses). ^{*a*}The reaction was carried out at 60 °C. ^{*b*}The reaction was carried out at 60 °C using a catalyst loading of 5 mol %. ^{*c*}At 65 °C using 2 equiv. of NIS. ^{*d*}At 65 °C using 3 equiv. of NIS. ^{*e*}At 40 °C using 3 equiv. of NIS.

ed in very good yields.

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Mechanistic investigations were then undertaken. First, we studied whether iridacycles in oxidation state +3 are intermediates. When 1a was treated with a superstoichiometric amount of II (1.1 equiv.) at 40 °C in HFIP, an iridacyclic structure was formed and characterized by ¹H NMR spectroscopy (See SI). The iridacycle thus prepared could not be isolated. We therefore prepared DMSO-stabilized iridacycle 6a instead (Scheme 4a).¹⁶ Reaction of 6a with NIS at 0 °C gave, within a few minutes, 2a (Scheme 4b). Furthermore, when 6a was used as a catalyst (Scheme 4c), the results did not differ from those obtained with II. The reversibility of the C-H activation was confirmed when a 1:1 mixture of iridacycle 6a and 2-chlorobenzoic acid 1c was reacted in HFIP at 40 °C (Scheme 4d and SI). After 1 h, a mixture of both carboxylic acids 1a and 1c, as well as iridacycles, 6a and 6c was observed. Similar results were obtained when 6a was reacted with carboxylic acids 1e or 1f (See SI, S27).



When comparing the iodination rates of **6a** in different solvents, it was observed that the reaction was significantly accelerated in HFIP (Scheme 5).

A KIE (kinetic isotope effect) of 2.90 ± 0.36 was obtained when comparing the rate of **1a** to that of **1a**- d_1 (Scheme 6 and Figures S5-S6) under noncompetition conditions. The reversibility of the C–H activation (*vide supra*, Scheme 4d) is in agreement with the magnitude of this KIE. The high iodination rate of iridacycle **6a** (Scheme 4b), together with the KIE, indicates that the C–H bond is broken in the ratelimiting step (rls).

To obtain further information, DFT calculations were carried out using M06/6-311G** (SDD for Ir, I) with a solvation model (IEFPCM, solvent = TFE). Initially, taking the iridacycle **SM** as the reference, *and in the absence of HFIP*, activation energies of 21.8, 25.6 and 23.5 kcal/mol were computed for the oxidative addition, reductive elimination and C–H activation, respectively (SI). The reductive elimination

nation is the slowest step (25.6 kcal/mol), which is inconsistent with the C–H bond being broken in the rls.

These data are intriguing and could be related with the fact that the experimental results were substantially better when



Scheme 5. Iodination of 6a in different solvents.



Scheme 6. KIE determination.

the reactions were carried out in HFIP, as opposed to other solvents (Table 1 and Scheme 5). The similarity of the activation energies of the three steps, and the crucial role of HFIP suggest a complex mechanism involving a change in rls depending on the reaction conditions. It has been demonstrated that fluorinated alcohols can be exceptional reaction media for various transformations, including C-H activations.²⁴ Therefore, the cycle was re-computed in the presence of HFIP, which can form H-bonds with NIS,²⁵ facilitating or disabling the different steps of the reaction. The E_a of the three consecutive steps now became 21.4, 20.0 and 23.6 kcal/mol, respectively (Figure 1). The electron withdrawing effect of the H-bonding with HFIP²⁶ was found to destabilize preferentially Ir(V) intermediate INT-2 (resting state in the absence of HFIP, see SI), thus reducing the E_a of the reductive elimination (**TS-RE**), and accelerating the reaction. This agrees well with the kinetic profile of the reaction of **6a** with NIS in different solvents (Scheme 5 and Table 1). The C-H activation step then becomes the rls (TS-CH, 23.6 kcal/mol) and occurs via a concerted metalation-deprotonation (CMD) pathway,²⁷ agreeing well with the excellent results obtained in the absence of any base, and explaining the superior activity in HFIP as the solvent (Table 1).[¶] Futher attempts to support the proposed mechanism resulted in the characterization by ¹H NMR spectroscopy of an additional iridacycle, formed exclusively upon addition of NIS, and that may be assigned to INT2 (see SI). An alternative mechanism without involving Ir(V) intermediates in which the iridacycle

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species are directly iodinated, was also considered. However, we could not locate any effective TS below 30 kcal/mol for



Figure 1. Catalytic cycle. The energy values correspond to Free energies in kcal/mol.

that process.

3. CONCLUSION

In summary, a very efficient catalytic method for the iodination of benzoic acids has been developed. A simple Ir(III) complex is used, which, under very mild reaction conditions and in the absence of any additive or base, selectively gives *o*-iodinated carboxylic acids in excellent yields when HFIP is used as the solvent. Air and moisture are well tolerated. The mechanism for this mild C–H iodination involves a rate-limiting metalation, followed by iodination through an Ir(III)/Ir(V) catalytic cycle. Most importantly, we present for the first time strong evidence explaining the unique role of the solvent HFIP in this C–H activation; upon formation of H-bonds, HFIP is able to lower the activation energy of the reductive elimination step. These studies may contribute to develop an understanding of the beneficial effect of using HFIP as the solvent in catalytic reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterization of the products are available free of charge via the Internet at http://pubs.acs.org

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NOTES

¥ In contrast with the work reported by Yu and co-workers, the iridium system reported here affords selectively monoiodinated products from *meta*-substituted benzoic acids. This selectivity may be due to the milder reaction conditions used here.

§ Phenylacetic acid under the optimal reaction conditions gave only 10% yield of 2-iodophenylacetic acid. The low ability of the CH₂CO₂H functional group to direct the iodination enables selective formation of **2i** from dicarboxylic acid **1i**.

¶ The lower reactivity of electron-poor carboxylic acids 1e and 1f, when compared to that of 1a, can be explained as a result of a decreased electron density on the iridium (III) center, reducing its ability to effectively undergo oxidative addition to form the Ir(V) intermediate, as confirmed computationally (see SI).

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