

A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

GDCh

International Edition

www.angewandte.org

Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202103269

Link to VoR: <https://doi.org/10.1002/anie.202103269>

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Palladium-Catalyzed Decarbonylative Iodination of Aryl Carboxylic Acids Enabled by Ligand-Assisted Halide Exchange

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In memory of Prof. Klaus Hafner.

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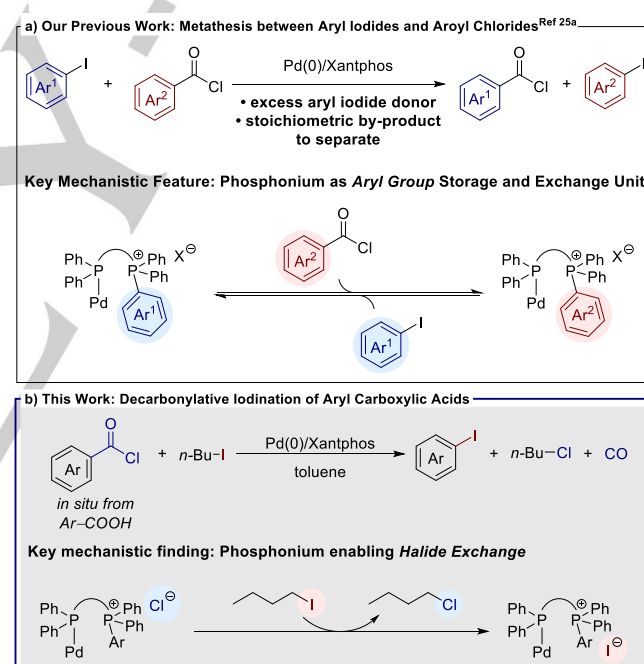
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Abstract: We report an efficient and broadly applicable palladium-catalyzed iodination of inexpensive and abundant aryl and vinyl carboxylic acids via *in situ* activation to the acid chloride and formation of a phosphonium salt. The use of 1-iodobutane as iodide source in combination with a base and a deoxychlorinating reagent gives access to a wide range of aryl and vinyl iodides under Pd/Xantphos catalysis, including complex drug-like scaffolds. Stoichiometric experiments and kinetic analysis suggest a unique mechanism involving C–P reductive elimination to form the Xantphos phosphonium chloride which subsequently initiates an unusual halogen exchange by outer sphere nucleophilic substitution.

Introduction

Organic halides are among the most prevalent functional groups in organic chemistry, spanning occurrence from natural products,^[1] pharmaceuticals,^[2] agrochemicals,^[3] to functional materials^[4] and molecular recognition.^[5] In addition, halides are important building blocks in organic chemistry and serve as synthetic handles, e.g. through carbon-halogen bond activation by transition-metals,^[6] metal-halogen exchange,^[7] or nucleophilic substitution.^[8] Numerous methods for the ruthenium-,^[9] rhodium-,^[10] nickel-,^[11] copper-catalyzed,^[12] and transition-metal free^[13] C(sp²)-halogen bond formation have been described.^[6] Over the last decades, Pd(0)/Pd(II) catalysis has emerged as an attractive alternative to those protocols, since it allows for mild reaction conditions and broad substrate scopes.^[14] Systematic stoichiometric studies by Hartwig on the reductive elimination of aryl-Pd(II)-halide complexes have paved the way to a more benign synthesis of aryl halides.^[15] Subsequent reports by the groups of Buchwald, Sanford and others have broadened the spectrum of accessible Pd(0)/Pd(II) catalyzed methods for the installation of carbon-halogen bonds.^[6,16] Among aromatic halides, aryl iodides take a privileged role, since they exhibit unique characteristics, such as superior reactivity in cross-coupling reactions,^[17] or their potential application in hypervalent iodine chemistry.^[18] Despite recent progress on the transition-metal catalyzed installation of carbon-halogen bonds,^[6,11a,b,f,12c,d]

general and mild methods for the installation of C(sp²)-I bonds remain highly sought after.



Scheme 1. Context of this work.

Since carboxylic acids are inexpensive, readily available, and ubiquitously found in natural products,^[19] their utilization as synthetic handles, e.g. through decarbonylative or decarboxylative pathways,^[20,21] holds great prospects in streamlining target-oriented synthesis. Given those advantages of carboxylic acids and the high synthetic utility of aryl iodides, the direct conversion of aryl carboxylic acids into aryl iodides would be a highly valuable transformation. Several protocols for the decarboxylative and decarbonylative iodination of aryl carboxylic acids have been developed since the initial report of the Hunsdiecker reaction.^[22,23,24] However, current reactions still exhibit several drawbacks: they either require preactivation of the carboxylic acid,^[23b] stoichiometric amounts of transition metal,^[23c,d] or a tailor-made Ir-photocatalyst for the installation of

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the carbon–iodine bond.^[23b,e] In addition, several reports show limited substrate scope,^[23f,g] or afford the desired aryl iodides in only modest yields.^[23h] Larrosa *et al.* disclosed an elegant transition-metal free protocol for the iodination of aryl carboxylic acids, using potassium phosphate and molecular iodine.^[24] However, the scope was mostly limited to electron-rich substrates with *ortho*-substituents or substrates with several fluorine substituents. For example, simple benzoic acid and *para*-nitro benzoic acid completely shut down the reaction. Additionally, diiodination via C–H iodination was observed in several cases.

In 2018, our group disclosed a single-bond metathesis reaction for the synthesis of aryl iodides from acid chlorides (Scheme 1a).^[25] It was proposed that a central, reversible C–P reductive elimination with the Xantphos ligand enabled the aryl group exchange between aryl iodides and aroyl chlorides. Therein, the mechanistic studies suggested that Xantphos acts as an aryl group storage unit to mediate facile aryl ligand exchange rather than either halide or CO exchange. In addition to the required activation step to transform the carboxylic acid into the acid chloride, excess amount of the iodination reagent was necessary in many cases to drive the reaction to high conversion. Furthermore, stoichiometric acid chloride by-product was generated during the reaction, complicating the purification of the desired aryl iodide.

Based on the ability of the Pd/Xantphos catalyst system to facilitate reductive elimination of C–I bonds,^[14a,25a] we hypothesized that broadly available aryl carboxylic acids could be transformed into aryl iodides using readily available iodide sources after *in situ* activation of the carboxylic acid to the acid chloride. This process could unlock an exciting and more general decarbonylative iodination of carboxylic acids (Scheme 1b). Herein, we report a palladium-catalyzed decarbonylative iodination of aryl and vinyl carboxylic acids using 1-iodobutane as iodide source via *in situ* formation of an acid chloride. Additionally, we report preliminary kinetic and organometallic studies which support the unique mechanism of this reaction. A strategic C–P reductive elimination with the ligand to form a phosphonium chloride provides an efficient and unusual platform to facilitate chloride/iodide exchange with the alkyl iodide in an outer sphere nucleophilic substitution.^[26]

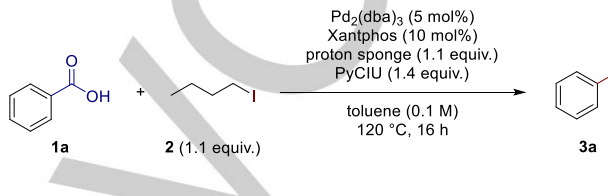
Results and Discussion

Evaluation of Reaction Conditions.

We began our investigations with benzoic acid (**1a**) and different iodide sources. Initial attempts with (alkali metal) iodide salts resulted in moderate conversion of the carboxylic acid to the desired iodobenzene (**3a**) (Table 1, entry 2 and 3). We reasoned that the palladium catalyst might be deactivated via the formation of unreactive PdI₂, resulting in low turnover numbers, thus revealing the necessity to slowly release iodide into the system. After extensive screening of the reaction conditions (see Supporting Information), it was found that alkyl iodides proved to be competent iodide sources, with iodomethane giving iodobenzene (**3a**) in 32% GC-yield (entry 4). Further careful optimization of the reaction parameters led to a combination of Pd₂(dba)₃, Xantphos, 1,8-bis(dimethylamino)naphthalene (proton sponge), 1-(chloro-1-pyrrolidinylmethylene)pyrrolidinium hexafluorophosphate (PyCIU) and less volatile 1-iodobutane in toluene at 120 °C, giving the desired iodobenzene (**3a**) in 88%

GC-yield after 16 hours (Table 1, entry 1). Running the reaction in an open system proved to be crucial to achieve high yields, presumably by helping the release of CO (entry 5). Xantphos, a wide bite-angle bidentate phosphine ligand previously employed in challenging reductive elimination steps,^[14a,20n,25,27,28] showed superior results among all the ligands tested (entry 6). For the *in situ* activation of the carboxylic acid, the combination of proton sponge as base and PyCIU as deoxygenating reagent gave the best result (entries 7–9).^[29] Switching to other Pd(0) precursors and solvents had a deleterious effect on the reaction yield (entries 10 and 11).

Table 1. Selected Optimization Data for the Iodination of Aryl Carboxylic Acids.^[a]



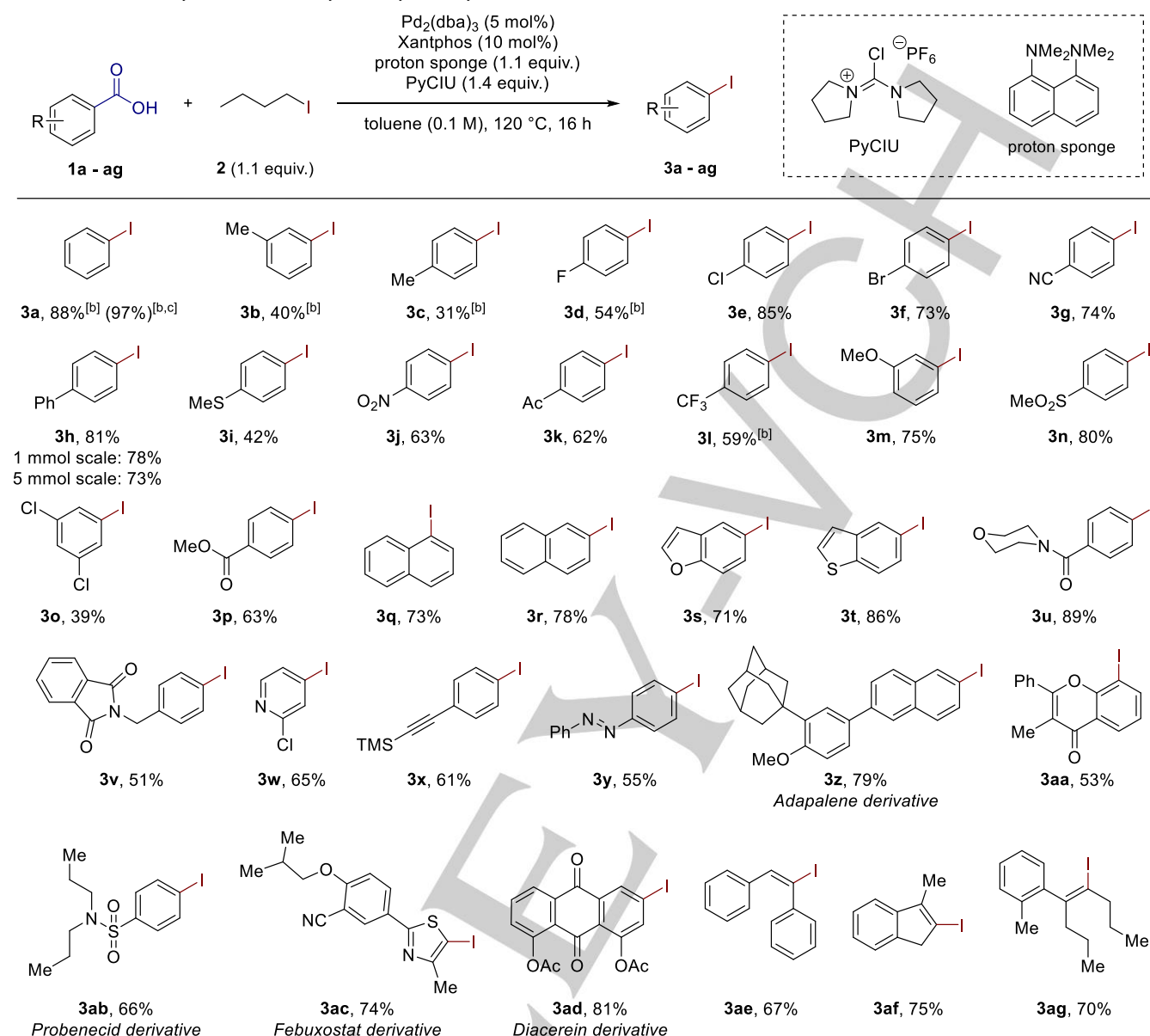
Entry	Deviations from above	Yield of 3a [%] ^[b]
1	none	88
2	LiI instead of 1-iodobutane	40
3	N ⁺ Bu ₄ I instead of 1-iodobutane	37
4	MeI instead of 1-iodobutane	32
5	Closed 4 mL vial instead of open system	10
6	P ^t Bu ₃ (20 mol%) instead of Xantphos	<5
7	DIPEA instead of proton sponge	13
8	2.0 equiv. proton sponge	76
9	Ghosez's reagent instead of PyCIU/proton sponge	64
10	Pd(PPh ₃) ₄ instead of Pd ₂ (dba) ₃	62
11	1,4-dioxane instead of toluene	32

[a] Reaction conditions: benzoic acid (0.25 mmol), 1-iodobutane (0.275 mmol), Pd₂(dba)₃ (5 mol%), Xantphos (10 mol%), 1,8-bis(dimethylamino)naphthalene (proton sponge, 0.275 mmol), 1-(chloro-1-pyrrolidinylmethylene)pyrrolidinium hexafluorophosphate (PyCIU, 0.35 mmol), toluene (2.5 mL), 120 °C, 16 h. [b] Yields in % obtained by GC-FID using *n*-dodecane as internal standard.

Iodination of Aryl and Vinyl Carboxylic Acids.

With these optimized reaction conditions, we set out to explore the generality of this reaction. A broad range of aryl carboxylic acids worked efficiently under the reaction conditions. Indeed, both electron-neutral (**3a**, **3r**) and electron-deficient (**3d**, **3g**, **3j**–**l**, **3n**, **3p** and **3u**) substituents were tolerated, giving the corresponding aryl iodides in moderate to very good yields (54–88%). The fact that simple electron-neutral (such as **1a**) and electron-poor aryl carboxylic acids (such as **1g**, **1j** and **1l**) could be converted into the corresponding aryl iodides (**3a**, **3g**, **3j** and **3l**) in good yields shows the orthogonality of this method to other previously reported methods,^[24] where electron-neutral or electron-deficient arenes gave low yields (in the case of **3g** and **3l**) or did not work at all (**3a** and **3j**). Carboxylic acids with electron-rich functional groups in *para*-position (**3c**, **3i**) were also tolerated, albeit affording the corresponding iodobenzene in lower yield (31% and 42%, respectively). In those cases, increased amounts of iodobenzene (**3a**) were observed as side product potentially due to scrambling with the phenyl groups of Xantphos. Moving the electron-donating group to the *meta*-position (**3b**, **3m**) partially restored the reactivity.

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Table 2. Palladium-catalyzed iodination of Aryl and Vinyl Carboxylic Acids.^[a]

[a] Reaction conditions: benzoic acid (0.25 mmol), 1-iodobutane (0.275 mmol), $\text{Pd}_2(\text{dba})_3$ (5 mol%), Xantphos (10 mol%), 1,8-bis(dimethylamino)naphthalene (proton sponge, 0.275 mmol), 1-(chloro-1-pyrrolidinylmethylene)pyrrolidinium hexafluorophosphate (PyCIU, 0.35 mmol), toluene (2.5 mL), 120 °C, 16 h. [b] GC-yield using *n*-dodecane as internal standard. [c] Starting from benzoyl chloride (0.25 mmol) without PyCIU and proton sponge.

Several substrates bearing other halogen substituents (**3e**, **3f** and **3o**) afforded the corresponding aryl iodides in moderate to good yields, without any signs of either halogen exchange of other C–X bonds or catalyst deactivation by oxidative addition into the other carbon-halogen bonds. Substrates bearing *ortho*-substituents did not afford the desired aryl iodides in satisfying yields, and only activated *ortho*-substituted substrates, such as 1-naphthoic acid (**1q**), were converted to the corresponding iodides, giving 1-iodonaphthalene (**3q**) in 73% yield. Heterocycles, such as pyridine (**3w**), benzofuran (**3s**), or benzothiophene (**3t**) were well-tolerated under the reaction conditions. A protected benzylic amine (**3v**), a TMS-protected alkyne (**3x**), and an azo-group (**3y**) further demonstrate the broad functional group tolerance of this reaction.

Carboxylic acids are ubiquitous in natural products and bioactive molecules.^[19] Our method for the efficient conversion of aryl carboxylic acids into aryl iodides is therefore highly desirable, as the carbon–iodine bond can then serve as a platform to access a plethora of different functional groups. To further highlight the synthetic versatility of our method, several complex carboxylic acids, some of which are used as drugs, were subjected to the reaction conditions. Adapalene (**1z**) and a flavone derivative (**1aa**) gave the corresponding iodoarenes **3z** and **3aa** in 79% and 53% yield, respectively. Probenecid and Febuxostat also were converted to the iodinated derivatives (**3ab**, 66% and **3ac**, 74%). Additionally, Diacerein, a drug for the treatment of osteoarthritis,^[30] cleanly reacted to the iodoarene derivative **3ad** in 81% yield. Our method also proved to be competent to convert vinyl carboxylic acids into the corresponding vinyl iodides, a class of compounds challenging to access otherwise.^[14a,16f] While

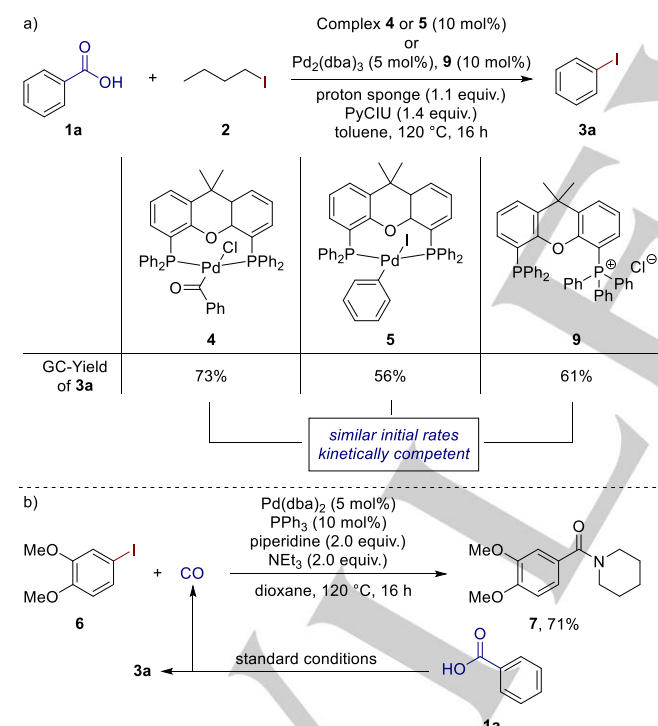
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simple cinnamic acid did not afford the product, α -phenylcinnamic acid afforded vinyl iodide **3ae** in 67% yield. Indene derivative **1af** gave the corresponding vinyl iodide in 75% yield and tetrasubstituted vinyl iodide **3ag** was obtained in 70% yield. Furthermore, conducting the reaction at a larger scale (1 and 5 mmol) using carboxylic acid **1h** provided a comparable yield of the iodoarene **3h**, thus illustrating the scalability of this reaction.

Mechanistic Studies

The observation that only Xantphos as ligand gave the corresponding aryl iodides in satisfying yields, and the use of alkyl iodides as rather unconventional iodide source prompted us to start investigating the mechanism of this decarbonylative iodination of aryl and vinyl carboxylic acids.

Previous reports have shown that the combination of proton sponge and deoxychlorinating reagent efficiently produces the acid chloride from the carboxylic acid.^[20h,29] We thus started our studies by synthesizing the oxidative addition complex **4** of Pd(Xantphos) into the carbon–chlorine bond of benzoyl chloride.^[25b,31] Additionally, complex **5**, resulting from the oxidative addition of Pd(Xantphos) into the carbon–iodine bond of iodobenzene was synthesized.^[31d,32] Both complexes proved to be kinetically competent under our standard reaction conditions (Scheme 2a, see Supporting Information for details) and are thus likely involved in the catalytic cycle.

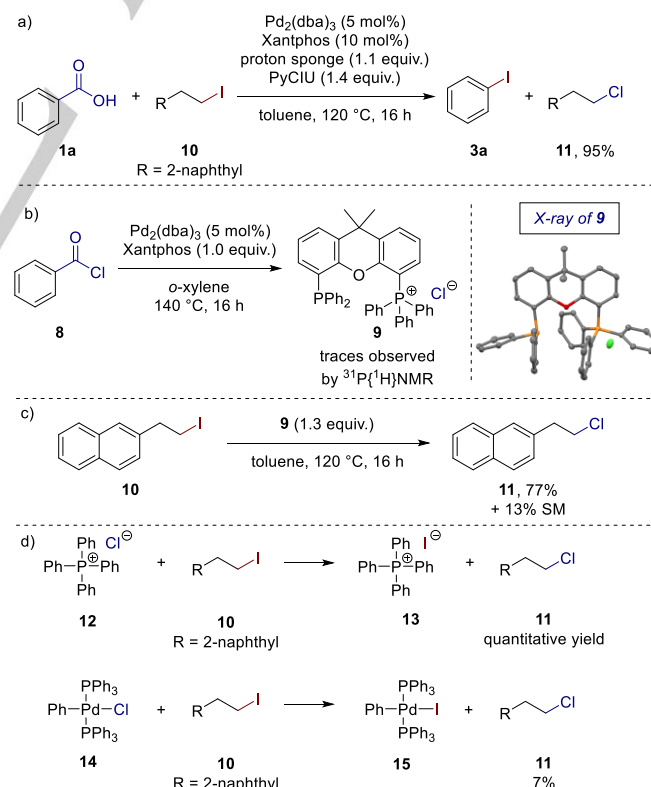


Scheme 2. a) Catalytic and kinetic competence of isolated complexes **4** and **5** and of Pd(0) with phosphonium chloride **9**. b) Detection of CO release by two-chamber aminocarbonylation.

We envisaged that after oxidative addition, complex **4** might lose CO. Consistent with this hypothesis is the requirement for open reaction conditions, suggesting that CO is detrimental to the process.^[16d,31e] To further support this hypothesis experimentally, we conducted a reaction in a sealed two-chamber system (Scheme 2b).^[33] In one chamber, our reaction for the iodination of carboxylic acids was run; the other chamber was loaded with 4-

iodo-1,2-dimethoxybenzene (**6**) under known conditions for the aminocarbonylation of aryl iodides.^[33] After 16 hours, product **7**, which stems from incorporation of CO released in the first chamber, was isolated in 71% yield. This result confirms that CO is released in our reaction. The need to release CO is consistent with previous reports showing that the formation of aryl-Pd-X (X = halogen) complexes is highly favored over aryl-Pd-X complexes in the presence of CO.^[27a,28,31e] Therefore, extrusion of CO from the reaction mixture is necessary to avoid CO re-insertion and to drive the equilibrium towards the aryl-Pd-X complex. Accordingly, the yield of iodobenzene (**3a**) in our standard reaction dropped significantly from 88% to 55%, when conducting the experiment under an atmosphere of CO (see Supporting Information).

During our optimization studies, 1-chlorobutane was observed by GC-MS analysis. This observation, paired with the absence of olefinic by-products and the fact that *tert*-butyl iodide hardly affords the desired product, iodobenzene (**3a**), speaks against a mechanism involving oxidative addition into the aliphatic carbon–iodine bond and β -hydride elimination to activate the reagent.^[27,34] To test this hypothesis, we synthesized heavier alkyl iodide 2-(2-iodoethyl)naphthalene (**10**) and subjected it to our standard reaction conditions. The corresponding halide exchange product – alkyl chloride **11** – could be isolated in 95% yield without any signs of olefinic by-products (Scheme 3a). This result indicates that a pathway via oxidative addition into the aliphatic carbon–iodine bond,^[34] and subsequent β -hydride elimination is not operating under our reaction conditions. We therefore hypothesized that, similarly to previous reports from our group,^[25a] complex **4** could undergo C–P reductive elimination after CO de-insertion to form a phosphonium chloride.



Scheme 3. a) Isolation of heavier alkyl chloride **10** under the standard reaction conditions. b) Phosphonium chloride **9** observed by ³¹P-NMR and X-ray structure of **9**. c) Nucleophilic substitution of heavier alkyl iodide with **9**. d) Nucleophilic substitution of heavier alkyl iodide **10** with tetraphenylphosphonium chloride **12** and with [(PPh₃)₂Pd(Ph)(Cl)] (**14**).

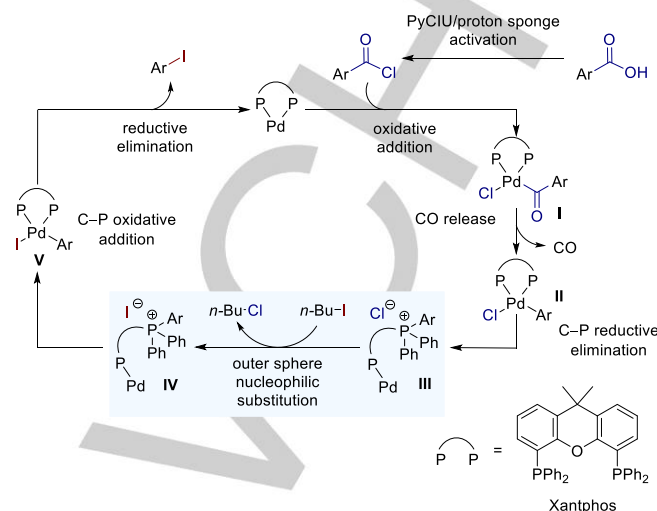
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The outer sphere chloride anion could then readily substitute the iodide of alkyl iodide **2** or **10** through a nucleophilic substitution reaction.^[35] Indeed, when we tried a stoichiometric reaction to detect the mono-phosphonium chloride form of Xantphos (**9**), traces of the salt were unambiguously observed by ³¹P{¹H}-NMR together with a significant amount of the deactivation complex, (Xantphos)PdCl₂ (Scheme 3b, see Supporting Information). We next used a different route to access phosphonium chloride **9** in preparative quantities, starting from chlorobenzene under nickel catalysis.^[36] The identity of the counter anion of **9** was confirmed by X-ray analysis. With this salt in hand, we then tried additional control reactions to support our hypothesis. First, phosphonium chloride **9** proved to be a kinetically competent ligand in our model reaction (see Scheme 2a and Supporting Information for details). Furthermore, heavier alkyl iodide **10** was reacted with phosphonium chloride **9**. To our delight, the corresponding alkyl chloride **11** was isolated in 77% yield, together with 13% unreacted starting material **10** (Scheme 3c), showing that the chloride counter ion of the phosphonium salt is indeed a competent reagent for nucleophilic displacement.

Still, it cannot be excluded from these experiments that the nucleophilic substitution might be mediated by a simple aryl-Pd-Cl complex in the absence of C–P reductive elimination. We therefore performed additional stoichiometric experiments to probe such a pathway. To facilitate the analysis of the reaction mixture, we chose tetraphenylphosphonium chloride (**12**) instead of phosphonium chloride **9**. First, the reaction of **12** with **10** to tetraphenylphosphonium iodide (**13**) and alkyl chloride **11** proved that the nucleophilic substitution is feasible and that the reaction reaches full conversion (Scheme 3d, top). Subsequently, alkyl iodide **10** was reacted with the synthesized complex [(PPh₃)₂Pd(Ph)(Cl)] (**14**).^[37] If this aryl-Pd-Cl complex, which is unknown to undergo C–P reductive elimination to form a phosphonium chloride,^[36] is less capable of facilitating the halide exchange than the phosphonium salts **9** and **14**, the yield of alkyl chloride **11** should be reduced. Indeed, the yield of alkyl chloride **11** reached only around 7%, even after prolonged reaction time (Scheme 3d, bottom). This observation suggests that a mechanism involving a direct reaction between an aryl-Pd-Cl intermediate and the alkyl iodide is unlikely.

Based on the results from our experiments, we propose a mechanism for the iodination of aryl and vinyl carboxylic acids that best explains all the findings (Scheme 4). After *in situ* activation of the carboxylic acid with the proton sponge and PyClU, facile oxidative addition of (Xantphos)Pd(0) into the C–Cl bond occurs to form complex **I**. Subsequent CO de-insertion and release gives complex **II**, which could undergo C–Cl reductive elimination to form aryl chlorides under certain conditions.^[16d] However, chlorobenzene was never observed during our studies and experiments suggest that complex **II** undergoes chemoselective C–P reductive elimination to afford **III**. At this point, it is unclear, whether CO release occurs before or after C–P reductive elimination and nucleophilic substitution. Arndtsen has shown that CO renders the Pd center more electron-deficient, facilitating analogous challenging reductive elimination steps,^[38] which could also be the case here in the C–P reductive elimination. Since the chloride anion is in the outer sphere in complex **III**, fast nucleophilic substitution occurs with the alkyl iodide to form complex **IV**, which now has iodide as counter anion. This complex then undergoes C–P oxidative addition to form complex **V**, followed by reductive elimination to release the desired aryl iodide

and close the catalytic cycle. In rare cases, phenyl group scrambling was observed after C–P oxidative addition into the phosphorus-phenyl bond of Xantphos to give iodobenzene (**3a**) (*vide supra*), thus further supporting the proposed mechanism.



Scheme 4. Proposed catalytic cycle for the palladium-catalyzed decarbonylative iodination.

Conclusion

In conclusion, we have reported a method for the decarbonylative iodination of readily available aryl carboxylic acids with 1-iodobutane. The generality of this transformation has been demonstrated on a wide spectrum of aryl carboxylic acids and on a number of drug molecules. In addition, electron-poor substrates which are not compatible with conventional iodination methods,^[24] were efficiently converted to their corresponding aryl iodides. For this operationally simple iodination process, mechanistic experiments and kinetic studies support a phosphonium halide intermediate which is key to enable a rapid halogen exchange via S_N2 type reaction with a primary alkyl iodide, revealing an unusual outer sphere nucleophile exchange process. To the best of our knowledge, this constitutes the first example of halide exchange assisted by C–P reductive elimination,^[9] followed by sequential nucleophilic substitution and oxidative addition at a Pd center.

Experimental Section

Experimental details and compound characterization are given in the supporting information.

Acknowledgements

This project received funding from the European Research Council under the European Union's Horizon 2020 research and innovation program (Shuttle Cat, Project ID: 757608), the FCI (scholarship to P.B.), LG Chem (scholarship to Y.H.L.), ETH Zürich, the Max-Planck-Society and the Max-Planck-Institut für Kohlenforschung. We thank the NMR service, the Molecular and Biomolecular Analysis Service (MoBIAS), and X-ray (SMoCC)

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service of ETH Zürich for assistance. We thank Marius Lutz and Miguel Rivero Crespo for assistance with the kinetic studies and our group for critical proofreading of the manuscript.

Keywords: iodination • palladium • shuttle catalysis • reaction mechanism • ligand non-innocence

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