$PhICl_2$ is activated by chloride ions

Tania, Tiffany B. Poynder, Aishvaryadeep Kaur, David J. D. Wilson and Jason L. Dutton*

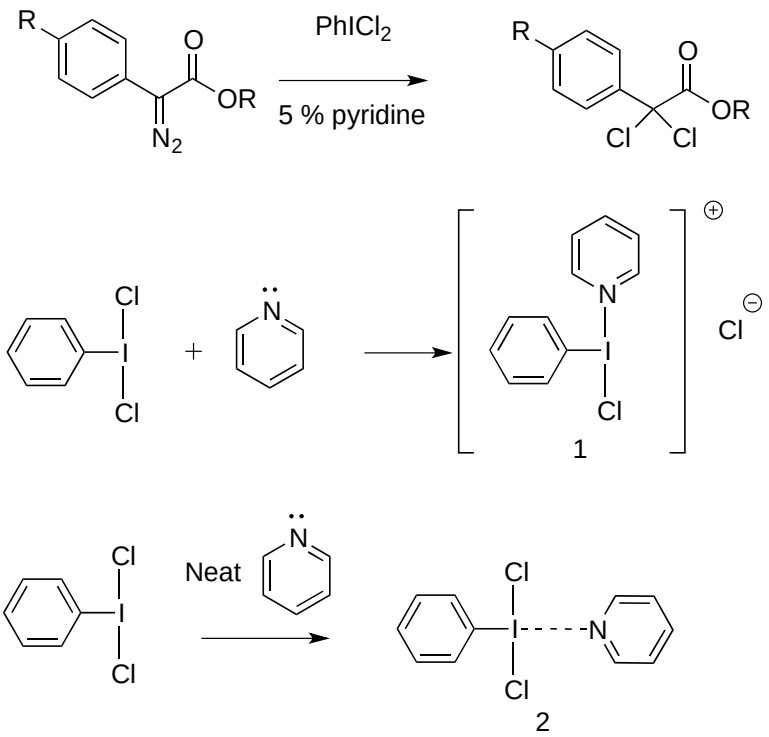
Department of Chemistry and Physics, La Trobe University, Melbourne, Victoria, Australia

j.dutton@latrobe.edu.au

ABSTRACT

A study on the potential activating role of pyridine in the electrophilic chlorination of anisole by $PhICl_2$ has led to the discovery that soluble sources of chloride ions activate $PhICl_2$ in the reaction at catalytic loadings, greatly increasing the rate of chlorination. It is further shown that presence of chloride increases the rate of decomposition of $PhICl_2$ into PhI and Cl_2. The specific mechanism by which chloride induces electrophilic chlorination and decomposition of $PhICl_2$ remains an open question.

$PhICl_2$ is a versatile I(III) oxidant, replacing inconvenient to handle Cl_2 gas in a variety of applications.[1-3] Being itself generated from PhI and Cl_2, it is necessarily a weaker oxidant than Cl_2 and is thus inert towards many substrates. Methods to activate $PhICl_2$ are known, one of which is the addition of catalytic pyridine, for which intermediate **1** was proposed as the activated species (Scheme 1) in the chlorination of diazo species, and has also been invoked in leading textbooks.[4-5] Denmark in a recent review proposed that the source of electrophilic chlorine could be either structure **1** or [Pyr-Cl][Cl] formed from decomposition of $PhICl_2$ by pyridine.[6] We have recently shown these are not viable potential intermediates; the reaction of $PhICl_2$ and pyridine yields a simple coordination complex with pyridine weakly bound to the iodine in $PhICl_2$ (**2**).[7]



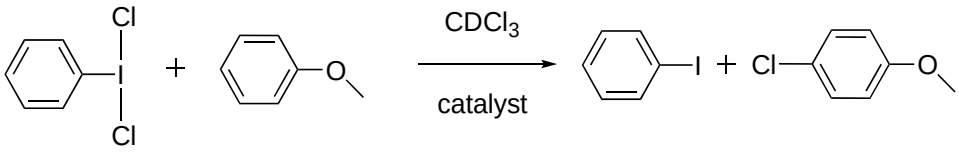
Scheme 1. Proposed (1) and experimentally determined (2) interaction of pyridine with $PhICl_2$.

The proposed intermediate (**1**) was not observed spectroscopically and was calculated to be 18 kJ/mol higher in energy than the weakly bound coordination complex. The properties of $PhICl_2$ in terms of charge distribution, bond distances, and MO energy levels were not found to be significantly perturbed by the coordination of pyridine.

While **1** can be excluded as the activated species, in the Murphy reports pyridine clearly acts as a catalyst by some means in the chlorination of diazo compounds by $PhICl_2$. Furthermore, pyridine is a very common additive, either in excess or catalytically, in a variety of reactions involving $PhICl_2$.[8-19] In many examples pyridine is clearly acting as a proton accepting base or the pyridine is proposed to be a catalyst, but in others there is no eliminated proton with nothing specific proposed about the role of pyridine.

We decided to investigate if pyridine could catalytically activate $PhICl_2$ in the electrophilic chlorination of an aryl ring, using anisole as a model aryl substrate. The addition of pyridine for this class of reaction with $PhICl_2$ has also been reported in the context of scale-up chemistry for chlorination of an activated aniline, using an excess of pyridine, where it could be acting as simply a base.[20]

The reaction between $PhICl_2$ and anisole in $CDCl_3$ at concentrations of 0.09 M was monitored by ^1H NMR spectroscopy with conversion to 4-chloroanisole and PhI determined by relative integration of the anisole methyl peak at t = 60 minutes. For the reaction of only $PhICl_2$ and anisole the conversion was measured to be 1% at 60 minutes and 23% after 20 hours.



Scheme 2. Chlorination of anisole with $PhICl_2$.

Addition of 20 mol% pyridine resulted in an increase in the conversion at t = 60 minutes to 77%, which indicates that pyridine is indeed facilitating this reaction *via* some mechanism at catalytic loading. However, the reaction itself generates HCl, which is observed in the ^{1}H NMR to protonate the pyridine. After the reaction has proceeded > 20%, all of the pyridine should be present as pyridinium chloride. Thus, pyridine cannot be only facilitating this reaction by acting as a nucleophile, as the pyridine itself is completely consumed before the reaction is finished.

Since pyridinium chloride becomes the dominant pyridine containing species in the reaction, we next tested its efficacy in activating $PhICl_2$ in the chlorination of anisole.

Addition of 20% pyridinium chloride to $PhICl_2$ and anisole resulted in a conversion of 92% at t = 60 minutes, higher than what was seen with pyridine. This observation led to the hypothesis that the activating agent is either pyridinium or chloride anions,; pyridinium could be activating $PhICl_2$ via hydrogen bonding with the I-Cl of $PhICl_2$, or chloride could be activating $PhICl_2$ via a nucleophilic interaction.

To control for hydrogen bonding 20% NBu_4Cl was added to the reaction of $PhICl_2$ and anisole. This resulted in a conversion of 93% at t = 60 minutes. The reaction with 20% pyridinium triflate, which should hydrogen bond to $PhICl_2$ equally as well as pyridinium chloride, gave a conversion of only 12%. 20% NBu_4OTf gave a conversion of 31%. Both of these results are higher than the baseline reaction with no additive, while the result with NBu_4OTf indicates that triflate is also activating $PhICl_2$, but more weakly than chloride.

Given these results we hypothesize that $PhICl_2$ is activated by chloride ions. In the reaction with 20% pyridine the activation is induced by the formation of HCl from inactivated $PhICl_2$, for which a small conversion to 4-chloroanisole occurs. The HCl is then converted into free chloride by protonation of the pyridine to give pyridinium chloride, whereby the free chloride then acts as a catalyst accelerating the reaction. To test this hypothesis 20 mol% by HCl of

2M HCl in ether was added to $PhICl_2$ and anisole, which gave a t = 60 minutes conversion of 1%, indicating that the chloride engaged with the proton in HCl is not an effective activating agent. This is also consistent with the sluggish reaction in the absence of a catalyst, as if HCl was effectively activating the $PhICl_2$ the HCl made as the reaction slowly proceeds should then act as a catalyst, accelerating the reaction and giving high conversion.

4-dimethylaminopyridine (4-DMAP) was also reported to catalytically activate $PhICl_2$, but we have previously shown that 4-DMAP immediately reacts with $PhICl_2$ to give 3-chloro-4-dimethylaminopyridine and protonated 4-DMAP as a chloride salt in an electrophilic aromatic substitution.[7, 15] This means that in such a reaction all the 4-DMAP is consumed rather than acting as a catalyst. Investigating this aspect, addition of 20% 4-DMAP to $PhICl_2$ and anisole gives a conversion of 80% to chlorinated anisole, showing catalytic activation, and excellent conversion considering that 10% of the $PhICl_2$ is immediately consumed by reaction with 4-DMAP. Addition of 20% protonated 4-DMAP as a chloride salt gives 99% conversion. Addition of independently synthesized 3-chloro-4-dimethylaminopyridine, produced in the reaction with 4-DMAP and $PhICl_2$, and a weaker base and nucleophile than 4-DMAP gives 81% conversion of anisole. Addition of the hydrochloride salt of 3-chloro-4-dimethylaminopyridine gives 98% conversion to 4-chloroanisole after t = 60 minutes.

Taken together this data supports that generation of free chloride in the reactions of $PhICl_2$ with anisole has a strong activating effect at catalytic loadings. A 20% loading of NBu_4Cl gives > 90% conversion within 5 minutes. Reduction of NBu_4Cl loading to a mole fraction of 5% gives a conversion of 68% after 5 minutes and 86% conversion after 20 minutes showing that it is effective at relatively low loadings.

Finally, we tested LiCl and NaCl as simple chloride sources. LiCl has minimal solubility in $CDCl_3$ but has excellent solubility in THF. However, we found that the chlorination reactions did not occur at all in THF, even with NBu_4Cl. Stirring a suspension of 20 mol% LiCl or

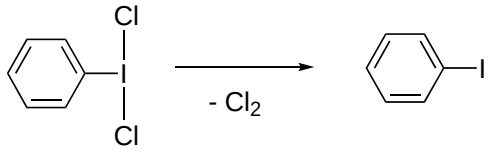
NaCl by weight in a $CDCl_3$ solution of $PhICl_2$ and anisole was found to give a conversion of 1% after 60 minutes, no improvement over no catalyst addition, indicating that soluble chloride is required.

Catalyst	Loading (mol %)	Conversion (%)
None	0	1
Pyridine	20	77
Pyridine.HCl	20	92
Pyridine.HOTf	20	12
Pyridine.HOTf	50	21
NBu_4Cl	20	93
$HCl.Et_2O$	20	1
NBu_4OTf	20	31
4-DMAP	20	80
4-DMAP.HCl	20	99
4-DMAP.HOTf	20	8
3-Cl-4-DMAP	20	81
3-Cl-4-DMAP.HCl	20	98
NBu_4Cl	5	86
NaCl	20	1
LiCl	20	1
LiCl	50	1

Table 1. Conversion of a 0.09M $CDCl_3$ solution of anisole to 4-chloroanisole after 60 minutes by equimolar $PhICl_2$ with the specified additive.

We next explored the decomposition of $PhICl_2$. A 0.09 M solution of $PhICl_2$ in $CDCl_3$ (in the absence of any other species), was constantly stirred and left open to the atmosphere to allow Cl_2 to escape, which led to $PhICl_2$ decomposing into PhI and Cl_2 with a conversion of 69% after 20 hours. In a shorter time-frame, the percentage decomposition at the specified time points is given in Table 2. To determine if chloride and the other considered species could be inducing decomposition of $PhICl_2$ the specified amount of additive was mixed with $PhICl_2$ and conversion into PhI monitored by ^1H NMR spectroscopy. The results are collated in Table 2, which shows that addition of catalytic amount of chloride in the form of NBu_4Cl induces a much more rapid decomposition of $PhICl_2$. Pyridinium hydrochloride also induces

an increased rate of decomposition, as does free pyridine although to a lesser extent that NBu_4Cl. 20 mol% HCl in ether did not result in an increased rate of decomposition, nor did a suspension of LiCl give a significant increase. Addition of NBu_4OTf and pyridinium triflate also results in an increased rate of decomposition over no additive but to a lesser extent than NBu_4Cl.



Time	Decomposition (%)							
	No additive	**20% Pyridine**	**20% Pyridine-HCl**	**20% Pyridine-HOTf**	**20% NBu_4Cl**	**20% HCl**	**20% NBu_4OTf**	**20% LiCl**
10 min	9	20	29	10	33	5	14	15
30 min	10	28	30	25	38	9	17	19
1 hr	13	33	33	30	42	14	25	25
2 hr	22	40	36	35	49	20	29	32
3 hr	27	48	40	40	56	23	30	37
4 hr	32	52	45	42	60	25	40	42
20 hrs	69	76	72	82	95	47	88	74

Table 2. Decomposition of a 0.09 M solution of $PhICl_2$ to PhI at the specified times as determined by ^1H NMR spectroscopy.

The chloride adduct to $PhICl_2$ has previously been reported in the context of crystallographic studies where the reaction of $[PPh_4][Cl]$ with $PhICl_2$ gives the salt $[PPh_4][PhICl_3]$.[21] The additional chloride completes a square planar geometry about the iodine with a much longer I-Cl interaction than is found along the Cl-I-Cl bond axis in the parent compound. No solution phase studies were reported. We were previously able to determine the binding constant between pyridine and $PhICl_2$ by ^1H NMR chemical shift differences in $PhICl_2$ using

the BindFit routine.[22] Addition of 1 equivalent of NBu_4Cl to $PhICl_2$ in $CDCl_3$ results in a distinct upfield chemical shift for the protons in the phenyl group of $PhICl_2$, which becomes more pronounced at increased loading. Using loadings of 1, 2, 3, 4, 5 and 10 equivalents of NBu_4Cl allowed for determination of the binding constant to be 0.62 M^{-1}. Triflate in the form of NBu_4OTf, which was found to be less activating towards $PhICl_2$ than chloride, was found to have a much smaller binding constant of 6.6 x 10^{-5} M^{-1} as expected for a weaker nucleophile.

Theoretical studies were carried out to investigate how chloride might activate and induce decomposition of $PhICl_2$. The B3LYP-D3(BJ)/def2-TZVPPD (SMD, chloroform) optimized geometry of the chloride adduct of $PhICl_2$, $[PhICl_3]^-$, is a four-coordinate complex, which may be described as a weakly bound complex of Cl^- and $PhICl_2$ analogous to the $PhICl_2$-pyridine complex **2**. The geometry of $PhICl_2$ is only minimally distorted by addition of chloride in $[PhICl_3]^-$, which is consistent with experimental structural studies. Comparing $[PhICl_3]^-$ to $PhICl_2$, the calculated I-C bond distance increases slightly from 2.109 to 2.141 Å and the I-Cl bond distances also increase slightly from 2.533 to (2.546 and 2.557) Å. The I-Cl bond trans to the phenyl ring arising from the additional chloride is longer than the other two at 2.978 Å owing to the strong trans effect of the phenyl group. This is in agreement with the experimentally determined bond distance of 3.02 Å.[21]

Similar to the pyridine adduct of $PhICl_2$, the calculated natural bond orbital (NBO) charge distribution in the $PhICl_2$ fragment is minimally perturbed by addition of the chloride. In a $CHCl_3$ solvent forcefield, the partial NBO charge on the iodine and chlorines in $PhICl_2$ are +1.027 and –0.506, respectively. In $[PhICl_3]^-$ a minimal change to +1.048 and (-0.515 and -0.525) is calculated. Plots of the electrostatic potential (Figure 1) illustrate the similarity of charge in the $PhICl_2$ moiety.

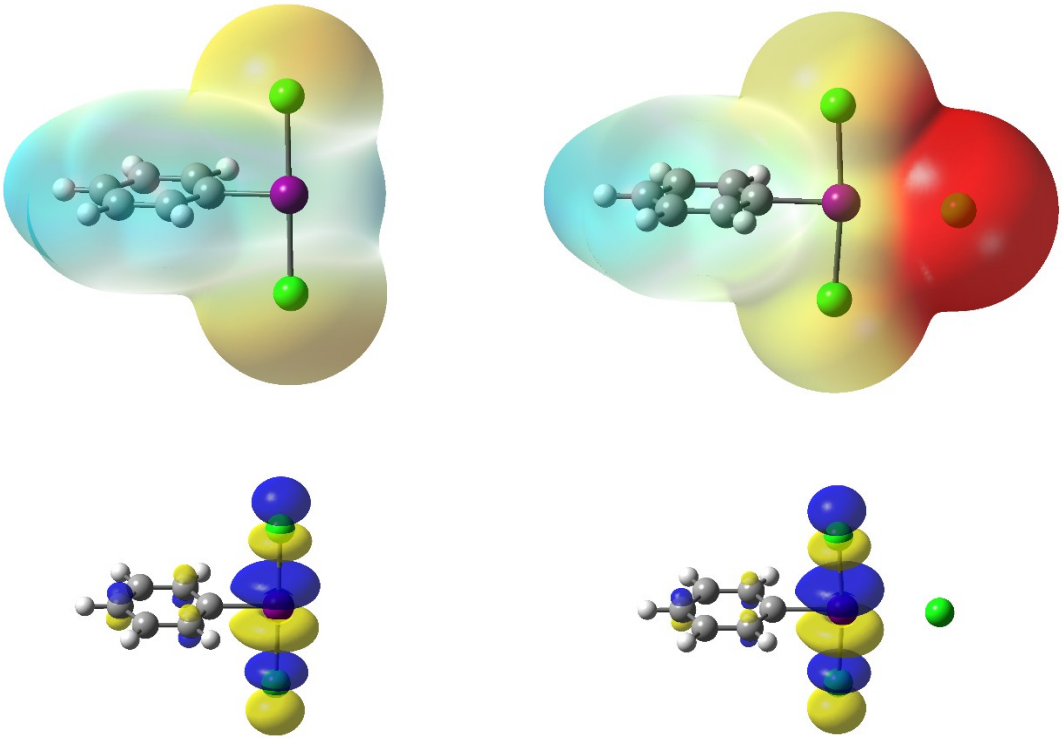


Figure 1. Plots of the electrostatic potential of $PhICl_2$ (left) and $[PhICl_3]^-$ (right) and the LUMOs and absolute energy levels in eV of $PhICl_2$ (left) and $[PhICl_3]^-$ (right) at B3LYP-D3(BJ)/def2-TZVPPD (SMD, chloroform).

Frontier molecular orbitals (Figure 1) indicate that the LUMO is centered on the Cl-I-Cl axis for both $PhICl_2$ and $[PhICl_3]^-$, which is destabilized in $[PhICl_3]^-$ by 0.83 eV. However, the increase in energy for the LUMO should make the electrophilic chlorine less reactive rather than more reactive, the opposite of what is observed experimentally. As extensive search of the potential energy surface around the Wheland intermediate in the chlorination of anisole from $PhICl_2$ revealed no transition state or other insight into what the mechanism might be.

It is clear from the decomposition studies that chloride alone induces the decomposition of $PhICl_2$ (into PhI and Cl_2) at catalytic amounts in the absence of the anisole substrate.

The potential energy surface of the system was examined to investigate if chloride might reduce the transition state barrier for this reaction. The calculated free energy of addition of Cl^- to $PhICl_2$ giving $[PhICl_3]^-$ was found to be close to zero, with values ranging from -3.4 to +6.3 kJ/mol depending on the method and basis set. At the highest level of theory utilized (DLPNO-CCSD(T)/ma-def2-QZVPP level of theory with a $CHCl_3$ solvent forcefield), ΔG was calculated to be +6.3 kJ/mol (+3.6 with dichloromethane solvation), in line with the experimentally determined binding constant of 0.62 M^{-1}.

Unfortunately, again despite clear experimental evidence that chloride accelerates the decomposition of $PhICl_2$ into PhI and Cl_2, no transition state from $[PhICl_3]^-$ or adding chloride along the Cl-I-Cl bond axis was located that gave a barrier consistent with the observed rate of the room temperature decomposition.

We have demonstrated that chloride ions act as an effective catalyst for the electrophilic chlorination of anisole using $PhICl_2$, and that catalytic chloride hastens the decomposition of $PhICl_2$. The mechanism for the reaction is yet unknown. Lupton[23] and later Nagib[24] reported that PhI(OAc)(Cl) is an activated chlorination reagent, and can be generated from $PhICl_2$ and acetic acid, or $PhI(OAc)_2$ and nucleophilic chloride sources, but in our case nucleophilic chloride with $PhICl_2$ would be substituting like for like. We are currently investigating this as well as the scope of $PhICl_2$ reactivity that can be accelerated with catalytic chloride.

We thank La Trobe University and the Australian Research Council (FT16010007, DP200100013) for their generous funding of this work. We thank Dr. Craig Fraser for obtaining ^1H NMR spectra of NBu_4Cl while we were in COVID lockdown and Dr. Conrad

Goodwin for the suggestion to try LiCl. We acknowledge generous allocations of computing time from NCI, Intersect, and La Trobe University.

REFERENCES

1. Yoshimura, A.; Zhdankin, V. V., Advances in synthetic applications of hypervalent iodine compounds. *Chem. Rev.* **2016,** *116*, 3328-3435.
2. Zhdankin, V. V.; Stang, P. J., Chemistry of polyvalent iodine. *Chem. Rev.* **2008,** *108*, 5299-5358.
3. Sousa e Silva, F. C.; Tierno, A. F.; Wengryniuk, S. E., Hypervalent iodine reagents in high valent transition metal chemistry. *Molecules* **2017,** *22*, 780-834.
4. Tao, J.; Tran, R.; Murphy, G. K., Dihaloiodoarenes: Dihalogenation of phenylacetate derivatives. *J. Am. Chem. Soc.* **2013,** *135*, 16312-16315.
5. Varvoglis, A., *The organic chemistry of polycoordinated iodine*. VCH: New York, 1992.
6. Cresswell, A. J.; Eey, T. C.; Denmark, S. E., Catalytic, stereoselective dihalogenation of alkenes: challenges and opportunities. *Angew. Chem. Int. Ed.* **2015,** *54*, 15642-15682.
7. Poynder, T. B.; Orue, A. I. C.; Tania; Sharp-Bucknall, L.; Flynn, M. T.; Wilson, D. J. D.; Arachchige, K. S. A.; Clegg, J. K.; Dutton, J. L., On the activation of PhICl2 with pyridine. *Chem. Commun.* **2021,** *57*, 4970-4973.
8. Wicha, J.; Zarecki, A.; Kocor, M., Oxidation of secondary alcohols to ketones by means of iodobenzene dichloride and pyridine. *Tett. Lett.* **1973,** *37*, 3635-3638.
9. Zarecki, A.; Wicha, J.; Kocor, M., Reaction of iodobenzene dichloride with C5-C6 unsaturated steroids. *Tetrahedron* **1976,** *32*, 559-563.
10. Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B., Iodobenzene dichloride - an efficient reagent for preparation of nitrile oxides from aldoximes. *Synth. Comm.* **1991,** *21*, 1625-1629.
11. Back, T. G.; Dyck, B. P.; Parvez, M., 1,3-diselenatanes and 1,3-dithietanes derivedfrom camphor. Formation, structure, stereochemistry and oxidation to selenoxide and sulfoxide products. *J. Org. Chem.* **1995,** *60*, 703-710.
12. Ibrahim, H.; Kleinbeck, F.; Tongi, A., Catalytic asymmetric chlorination of B-keto esters with hypervalent iodine compounds. *Helv. Chim. Acta* **2004,** *87*, 605-610.
13. Zhao, X.; Zhang, C., Iodobenzene dichloride as a stoichiometric oxidant for the conversion of alcohols in carbonyl compounds; two facile methods for its preparation. *Synthesis* **2007,** *4*, 551-557.
14. Chen, J.; Zeng, X.; Middleton, K.; Zhdankin, V. V., Facile preparation and reactivity of polystyrene-supported (dichloroiodo)benzene: a convenient recyclable reagent for chlorination and oxidation. *Tett. Lett.* **2011,** *52*, 1952-1955.
15. Murphy, G. K.; Abbas, F. Z.; Poulton, A. V., Dichlorination of oxindole derivatives using (Dichloroiodo)-benzene. *Adv. Synth. Catal.* **2014,** *356*, 2919-2923.
16. Coffey, K. E.; Moreira, R.; Abbas, F. Z.; Murphy, G. K., Synthesis of 3,3-dichloroindolin-2-ones from isatin-3-hydrazones and (dichloroiodo)benzene. *Org. Biomol. Chem.* **2015,** *13*, 682-685.
17. Coffey, K. E.; Murphy, G. K., Dichlorination of alpha-diazo-beta-dicarbonyls using (dichloroiodo)benzene. *Synlett* **2015,** *26*, 1003-1007.

18. Hepples, C.; Murphy, G. K., Synthesis of 3,3-dichloro-2-oxindoles from isatin-3-p-tosylhydrazones and (dichloroiodo)benzene. *Tett. Lett.* **2015,** *56*, 4971-4974.
19. Zhao, Z.; Kulkarni, K. G.; Murphy, G. K., Synthesis of aryldihalomethanes by denitrogenative dihalogenation of benzaldehyde hydrazones. *Adv. Synth. Catal.* **2017,** *359*, 2222-2228.
20. Zanka, A.; Takeuchi, H.; Kubota, A., Large-scale preparation of iodobenzene dichloride and efficient monochlorination of 4-aminoacetophenone. *Org. Process. Res. Dev.* **1998,** *2*, 270-273.
21. Grebe, J.; Geiseler, G.; Harms, K.; Dehnicke, K., Synthese und Kristallstruktur von PPh4[PhICl3]. *Z. Naturforch. B* **1999,** *54b*, 140-143.
22. Thordarson, P., Determining association constants from titration experiments in supramolecular chemistry. *Chem. Soc. Rev.* **2011,** *40*, 1305-1323.
23. Ngatimin, M.; Gartshore, C. J.; Kindler, J. P.; Naidu, S.; Lupton, D. W., The alpha-halogenation of alpha,beta-unsaturated carbonyls and dihalogenation of alkenes using bisacetoxyiodobenzene/pyridine hydrohalides. *Tett. Lett.* **2009,** *50*, 6008-6011.
24. Fosu, S. C.; Hambira, C. M.; Chen, A. D.; Fuchs, J. R.; Nagib, D. A., Site-selective C-H functionalization of (hetero)arenes via transitent, non-symmetric iodanes. *Chem.* **2019,** *5*, 417-428.

TOC Figure