$[Ag]_2[B_{12}Cl_{12}]$ as a Catalyst in $PhICl_2$ Mediated Chlorination

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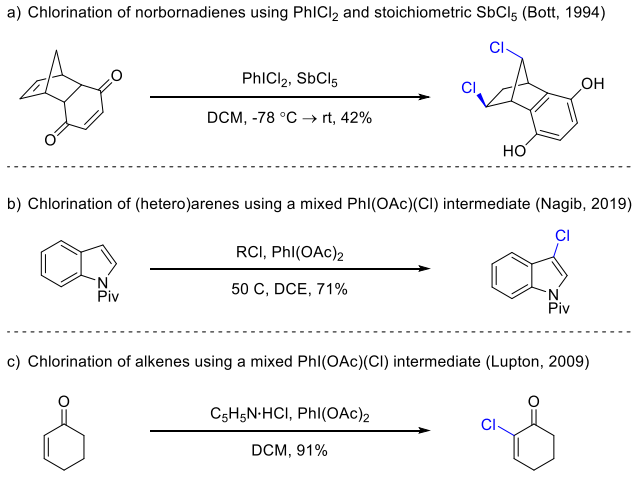
Abstract: The weakly coordinating $[B_{12}Cl_{12}]^{2-}$ originates from a family of carboranes typically reserved for application in coordination chemistry. Here, we show its readily accessible Ag(I) salt, $[Ag]_2[B_{12}Cl_{12}]$, can be used as a catalyst in the $PhICl_2$ mediated chlorination of arenes, alkenes, and alkynes. The promising activity displayed by $[Ag]_2[B_{12}Cl_{12}]$ over a variety of commercially available Ag(I) sources merits its incorporation to the toolkit of commonly screened silver catalysts in synthesis.

$PhICl_2$, the first reported λ^3-iodane compound,[1] is a versatile oxidant, primarily acting as a chlorinating agent representing a convenient substitute for Cl_2. Cl_2 is a highly corrosive, toxic gas, which in addition to being hazardous, is challenging to deliver in a stoichiometric fashion. Conversely, $PhICl_2$ is an easily weighed solid which is readily accessible from PhI, HCl, and H_2O_2,[2] can be used without the need for rigorously anhydrous conditions, and has been used widely in the oxidation of organic and inorganic compounds.[3]

$PhICl_2$, which can also be generated from a combination of PhI and Cl_2, is not without limitation. It is necessarily a weaker oxidizing agent than the Cl_2 it replaces and is unreactive towards many substrates. Activation of $PhICl_2$ can be accomplished using Lewis acids with a handful of reports over the years, including by stoichiometric $AgBF_4$ and $SbCl_5$ in chlorination of norbornene derivatives,[4] and by catalytic $AlCl_3$ in the replacement of diazo groups with chlorines.[5] Lewis acids such as BF_3 have also been shown to increase the activity of the related oxidant $PhI(OAc)_2$.[6] Numerous groups over the years have used TMS-OTf to generate purported $PhI(OTf)_2$ from $PhI(OAc)_2$ as a stronger oxidant,[7] however this has recently been shown to actually be PhI(OTf)(OAc).[8]

A recent paper by Nagib[9] described the activation of $PhI(OAc)_2$ using either HCl or acid chloride, or of $PhICl_2$ using acetic anhydride, in each case giving a mixed PhI(OAc)(Cl) species capable of chlorinating the C-H bonds of a variety of (hetero)arenes in a few hours at 50 °C. Lupton[10] employed the same concept a decade earlier using excess pyridinium chloride as the chloride source in concert with $PhI(OAc)_2$ to chlorinate α,β-unsaturated carbonyls and alkenes (Scheme 1).



Scheme 1. General classes of reported halogenation reaction using λ^3-iodanes.

In this report we show that abstraction of chloride from $PhICl_2$ using catalytic amounts of silver salts of the weakly coordinating anion $[B_{12}Cl_{12}]^{2-}$ increases the activity of $PhICl_2$ such that substrates unreactive or poorly reactive to $PhICl_2$ can be rapidly chlorinated at room temperature.

Our initial goal in this study was generation of the $[Ph\text{-}I]^{2+}$ dication, likely a highly reactive species. To achieve this we aimed to generate the $[Ph\text{-}I][B_{12}Cl_{12}]$ salt, using the weakly coordinating and highly robust nature of the $[B_{12}Cl_{12}]^{2-}$ dianion to allow for an isolable or at least observable species.[11] To this end, $PhICl_2$ was reacted with stoichiometric $[Ag]_2[B_{12}Cl_{12}]$ in $CHCl_3$. A ^{1}H-NMR spectrum of an aliquot of the reaction mixture revealed the presence of several species. Notably, similar reactivity was observed in the presence of catalytic (10 mol%) $[Ag]_2[B_{12}Cl_{12}]$. PhI and residual $PhICl_2$ appeared as the major components, alongside a set of minor signals which upon purification (see Supporting Information for details) were attributed to the formation of 4-chloro and 2-chloro-iodobenzene in an approximately 1:1 ratio. Addition of NEt_3 to the mixture resulted in the immediate precipitation of $[HNEt_3][Cl]$, indicating that HCl was generated during the course of the reaction. A solution of $PhICl_2$ in $CDCl_3$ left stirring in the absence of $[Ag]_2[B_{12}Cl_{12}]$ exhibited decomposition into PhI, with a PhI:$PhICl_2$ ratio of 1:4 after 16 h. Neither 4-chloro or 2-chloro-iodobenzene were observed in this experiment. (Scheme 2).

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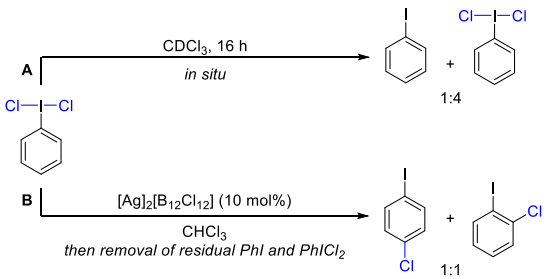
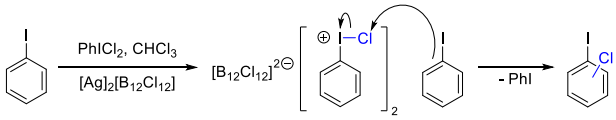


Scheme 2. A: $PhICl_2$ spontaneously degrades into PhI when left in solution. **B:** In the presence of $[Ag]_2[B_{12}Cl_{12}]$, spontaneous degradation is accompanied by minor amounts of 4-chloro and 2-chloroiodobenzene.

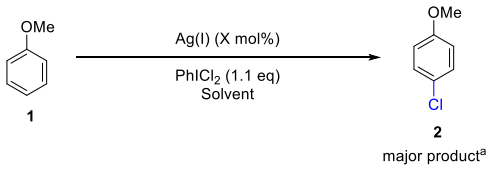
We have previously observed electrophilic aromatic substitution processes in reactions with electron poor λ^3-iodane species,[12] and therefore surmised that residual PhI generated from the decomposition of $PhICl_2$ was undergoing electrophilic aromatic chlorination. $[Ag]_2[B_{12}Cl_{12}]$ was essential for the reaction to proceed, suggestive of an "iodonium" type mechanism, in which Ag(I) abstracts a chloride from $PhICl_2$ resulting in a in an active $[PhICl]^+$ species, which is presumably stabilised by the weakly coordinating $[B_{12}Cl_{12}]^{2-}$ anion (Scheme 3). As discussed, attempts to isolate $[PhICl]^+$ or similar were unsuccessful.



Scheme 3. Proposed $[Ag]_2[B_{12}Cl_{12}]$ mediated "iodonium" mechanism for electrophilic aromatic chlorination of iodobenzene.

Encouraged by this preliminary reactivity, we decided to explore the efficacy of a number of other Ag(I) sources as mediators of electrophilic aromatic chlorination with $PhICl_2$ using the electron rich arene, anisole (**1**), as an exemplar substrate (Table 1).

Table 1. Exploration of a variety of in-house and commercially available Ag(I) sources in the electrophilic aromatic chlorination of anisole.



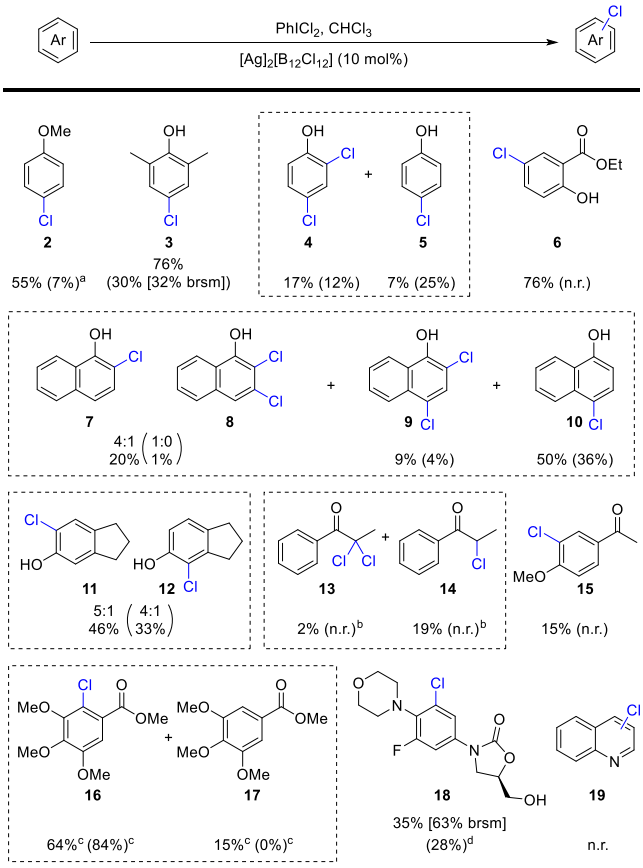
Entry	Catalyst	Loading (mol%)	Solvent	Conversion[b] (%)
1	none	n/a	$CDCl_3$	7%
2	$[Ag]_2[B_{12}Cl_{12}]$	5	$CDCl_3$	55
3	$[Ag]_2[B_{12}Cl_{12}]$	10	$CDCl_3$	67
4	$[Ag]_2[B_{12}Cl_{12}]$	10	CD_3CN	42
5	$[Ag]_2[B_{12}H_{12}]$	10	$CDCl_3$	61
6	$[Cs]_2[B_{12}H_{12}]$	10	$CDCl_3$	25
7	AgCl	20	$CDCl_3$	4
8	AgOTf	25	$CDCl_3$	6
9	AgOTf	100	$CDCl_3$	59
10	$AgBF_4$	25	$CDCl_3$	8
11	$AgBF_4$	100	$CDCl_3$	56
12	$AgSbF_6$	25	$CDCl_3$	46
13	$AgSbF_6$	100	$CDCl_3$	62
14	$AgNO_3$	100	$CDCl_3$	2

[a]Major observed isomer. [b]Conversion as determined by ^{1}H-NMR. All reactions monitored after 20 min at room temperature.

Only minor conversion to 4-chloroanisole (**2**) was observed in the absence of any catalyst (entry 1). As expected, addition of 5 mol% $[Ag]_2[B_{12}Cl_{12}]$ resulted in substantially greater reactivity, which was further improved to a conversion of 67% upon doubling catalyst loading to 10 mol% (entries 2 & 3). Pleasingly, conversion was rapid (20 minutes) and occurred readily at room temperature. Changing solvent to acetonitrile (entry 4), or altering the nature of the counteranion and cation (entries 5 & 6) were all detrimental. AgCl, potentially generated in quantities up to 20 mol% during the catalytic cycle with $[Ag]_2[B_{12}Cl_{12}]$, was also investigated as a potential catalyst, and resulted little conversion at 20% loading (entry 7). $[Ag]_2[B_{12}Cl_{12}]$ is synthesized from relatively inexpensive and non-toxic precursors, primarily $NaBH_4$, I_2, and SO_2Cl_2. The Ag(I) salt is most conveniently obtained by metathesis using $AgNO_3$ from a Cs salt. Unlike a number of related carborane reagents, which require the use of highly toxic and expensive reagents (i.e. $B_{10}H_{14}$),[13] and are extremely time consuming to make,[14] synthesis of $[Ag]_2[B_{12}Cl_{12}]$ is relatively straightforward, and can be delivered on a decagram scale in a few days in a typically equipped academic laboratory.[15] Nonetheless, it was considered prudent to investigate several commercially available Ag(I) sources as alternative activators of $PhICl_2$. Some conversion was observed in all cases, however activity was on the whole worse than $[Ag]_2[B_{12}Cl_{12}]$. Reactions with AgOTf, $AgBF_4$, and $AgSbF_6$ (traditionally considered weakly coordinating), displayed similar levels of activity only when stoichiometric quantities of Ag(I) were used (entries 9, 11, & 13, respectively). Lower loadings resulted in activity comparable to the use of no Ag(I) at all. $AgNO_3$ was the worst activator investigated, resulting in only minimal conversion even when deployed stoichiometrically (entry 14).

The optimum conditions (i.e. entry 3) were then applied to a range of substituted arenes in order to investigate the scope of the system. For each substrate, a control reaction (% yield in brackets) was also performed in the absence of $[Ag]_2[B_{12}Cl_{12}]$ to probe its innate propensity to react with $PhICl_2$ (Table 2).

Table 2. Substrate scope for $[Ag]_2[B_{12}Cl_{12}]$ catalysed electrophilic aromatic chlorination.



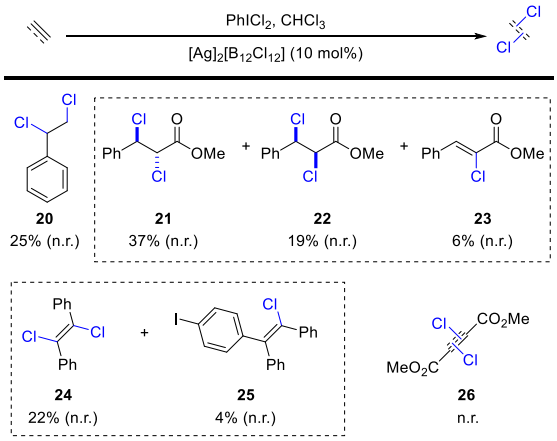
All yields correspond to isolation after column chromatography. Yields in brackets denote control experiments performed in the absence of $[Ag]_2[B_{12}Cl_{12}]$. Reactions were performed on a *c.a.* 0.5 mmol scale. n.r.: no reaction. [a]Conversion as determined by ^{1}H-NMR. [b]DCM used as solvent. [c]Isolated after esterification. [d]Recovery of starting material was unsuccessful.

Anisole translated well to scale, with 4-chloroanisole (**2**) isolated as the sole isomer in 55% yield. 2,6-Dimethyl phenol was also isolated exclusively as the 4-chloro isomer (**3**), and performed much better in the presence of catalyst (i.e. 76% vs. 30%). Selectivity and yields were lower for unsubstituted phenol, with the 2,4-dichloro isomer (**4**) isolated in higher proportions in the presence of catalyst. Incorporation of an electron withdrawing group to the phenol ring was well tolerated, as demonstrated by ethyl salicylate, which was chlorinated in the 4-position relative to the hydroxyl group (**6**). Notably, this reaction did not proceed at all in the absence of catalyst. Napthalen-1-ol proved problematic, with a range of isomers (**7**-**10**) isolated in either event, although the 4-chloro isomer (**10**) was the major in each case. Rerunning the

reaction at 0 ºC gave similar results and did not afford any improvement in selectivity. Using a phenol in which the 4-position was blocked gave a mixture of 2-chloro isomers (i.e. **11** and **12**). Interestingly, moving to propiophenone, an electron deficient arene, resulted exclusively in chlorination alpha to the ketone (**13** and **14**), with the aromatic ring left untouched. Introduction of an electron donating substituent marked a complete reversal in chemoselectivity (**15**). Neither substrate showed reactivity in a control reaction. 3,4,5-Trimethoxybenzoic acid, the most electron rich arene in the series, was the only member to display superior reactivity *in the absence* of catalyst, giving chloride **16** in 84% yield in a control experiment, but only 64% in the presence of $[Ag]_2[B_{12}Cl_{12}]$. The reason for this remains unclear, but may be explained, in part, by the propensity of residual PhI (generated as a byproduct of successful S_EAr) to undergo chlorination (as depicted in Scheme 2), thereby reducing the amount of $PhICl_2$ available for productive pathways. The conditions were also successful in delivering chlorinated oxazolidinone **18** as a single isomer, as confirmed by HSQC and subsequently X-ray crystallography. Compound **18** is a structural analogue of the commercially available antibiotic Linezolid,[16] and highlights the utility of this approach in late stage chlorination, an attractive strategy in drug design.[17] Finally, heteroarenes were investigated, and unfortunately proved to be a limitation. Quinoline was not amenable to chlorination (**19**). 4-Dimethylaminopyridine, which is contrast is electron rich and activated towards S_EAr, we have previously found is readily chlorinated without added Ag(I).[18] Pyridine gave a mixture of species for which only pyridnium chloride could be identified.

Given related methods (i.e. Nagib and Lupton) have both capitalised on PhI(OAc)(Cl), an active intermediate capable of delivering a single chlorine atom, and recent reports of the enantioselective dichlorination of alkenes,[19] we speculated whether our methodology would be capable of activating $PhICl_2$ to formally deliver a unit of molecular Cl_2. To this end, the chlorination of several alkenes/alkynes was investigated (Table 3).

Table 3. Substrate scope for $[Ag]_2[B_{12}Cl_{12}]$ catalysed chlorination of alkenes/alkynes.



All yields correspond to isolation after column chromatography. Yields in brackets denote control experiments performed in the absence of $[Ag]_2[B_{12}Cl_{12}]$. Reactions were performed on a *c.a.* 0.5 mmol scale. n.r.: no reaction.

Gratifyingly, this approach proved fruitful. Styrene delivered 1,2-dichloro styrene (**20**), albeit in modest yield. Methyl cinnamate was also readily chlorinated, giving the corresponding dichlorides (**21** and **22**) in a combined yield of 56% and a 2:1 d.r. in favour of the anti-isomer.[20] Minor amounts of the elimination product, methyl β-chlorocinnamate (**23**), were also isolated. Diphenylacetylene gave the corresponding *trans*-dichloride, **24**, as well as minor amounts of compound **25**, presumably arising as a result of nucleophilic attack of residual PhI to the less hindered side of the transient vinyl cation.[21] The structure of both compounds were confirmed by X-ray crystallography, with the trans-dichloride having been previously reported.[22] In all examples, the presence of $[Ag]_2[B_{12}Cl_{12}]$ was essential, and reactions were completely chemoselective for exocyclic π-bonds over arenes. The electron poor dimethyl acetylenedicarboxylate (DMAD), was not tolerated under these conditions, under which no chlorinated adducts (**26**) were observed.

In summary, we have demonstrated that catalytic $[Ag]_2[B_{12}Cl_{12}]$ can activate $PhICl_2$ to act as a source of Cl^+ in the electrophilic aromatic substitution of arenes, and also to deliver a full equivalent of Cl_2 in the chlorination of alkenes and alkynes. The reactions discussed herein likely proceed through the intermediacy of $[PhICl]^+$ *via* an "iodonium" mechanism, as opposed to a radical cation mechanism observed by others in related systems, and thereby present an attractive complimentary reactivity manifold.[9] Further evidence for this comes from the fact that electron rich arenes outperformed their electron poor counterparts, and that chlorination was generally selective for positions on which the greatest delocalisation of partial negative charge would be expected. Whilst innate reactivity was observed with some arenes, in all but one substrate surveyed, $[Ag]_2[B_{12}Cl_{12}]$ resulted in enhanced reactivity. Presence of the Ag(I) salt was essential for the chlorination of alkenes and alkynes.

Current usage of the $[B_{12}Cl_{12}]^{2-}$ dianion is largely limited to the inorganic community, where it enjoys a position amongst several related carborane reagents which act as superacids,[11] an unparalleled source of strong electrophiles,[23] and can be used in the isolation and X-ray crystallography of exotic carbocations.[24] It is our hope that in demonstrating the superior

activity of $[Ag]_2[B_{12}Cl_{12}]$ over several commonly used silver salts as a source of Ag(I), other practitioners will be encouraged to further investigate its application in related areas of organic synthesis.

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Keywords: iodine • hypervalent • oxidants • C-H functionalisation • weakly coordinating anion

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