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Alkali halides as nucleophilic reagent sources for N-directed palladium-catalysed *ortho*-C–H halogenation of *s*-tetrazines and other heteroaromatics†

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A general palladium-catalysed selective C–H halogenation reaction is reported, which was successfully achieved for a large variety of functionalized aromatic rings incorporating diverse N-directing groups. By using simple alkali halides of MX type as the nucleophilic reagent source (M = Li, Na, K, Cs and X = I, Br and Cl), and phenyliodanediacetate oxidant, clean C–H-iodination, bromination and chlorination reactions were performed. This general protocol of selective *ortho*-monohalogenation, which complements but contrasts with the classical methods using electrophilic reagents, is achievable in a short time (30 min) with microwave irradiation assistance. The reaction was extended to substrates bearing N-directing pyridine, pyrimidine, pyrazole, oxazoline, naphtho[1,2-*d*]thiazole, and azobenzene groups. Notably, the topical and selectivity-challenging *s*-tetrazine, as a nitrogen-rich heteroaromatic, was successfully halogenated by this protocol.

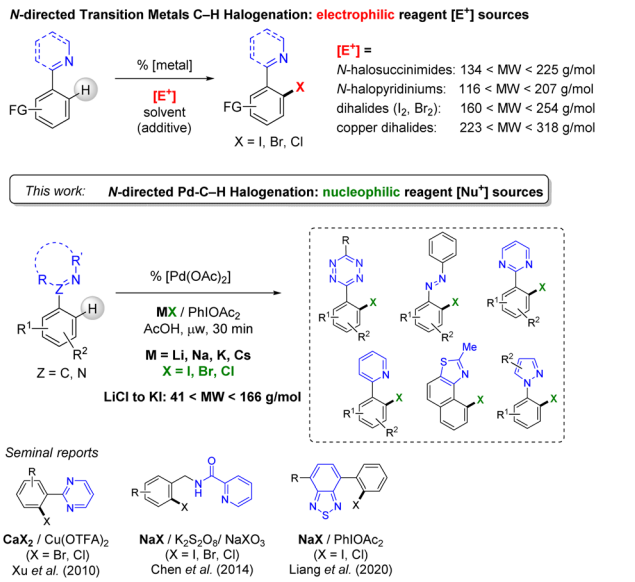
Introduction

Organic halides are essential synthetic precursors to reach highly functionalized pharmaceuticals, agrochemicals, and operative materials.[1] The synthetic and industrial routes to form these important building blocks, like heteroaromatic halides, generally involve multiple step reactions, often under harsh conditions.[2] The use of expensive and toxic reagents and solvents, under energy-consuming conditions, is an issue that is tackled by the search for more sustainable chemistry processes.[3] An alternative pathway to overcome the lack of selectivity encountered in the traditional organic halogenation protocols has been to exploit useful transmetallation processes such as boron-based,[4] albeit these are generally synthesized from an halide precursor, and in fine invariably generates undesirable stoichiometric metallic waste.

Ligand-directed C–H bond functionalization that is achieved by using the versatility of transition metal chemistry allowed much progress for the mild and selective introduction of halogens in synthetic organics (Scheme 1, top).[5] The number of synthetic steps is reduced, and so are the side-reactions and purification procedures.

The amount of waste is also minored by improving the regioselectivity of the functionalization, and the global tolerance to varied substituents. Following this strategy, our group and others illustrated the efficiency of palladium catalysts for the *ortho*-halogenation on different N-containing heteroarenes, including challenging substrates of high nitrogen-content.[5,6]

The current ligand-directed C–H halogenation approach has been mainly focused on the use of highly reactive preformed



Scheme 1 Electrophilic N-directed halogenation (top) and N-directed palladium-catalysed mono-halogenation using alkali halide nucleophilic sources (this work).

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electrophilic reagents such as N-halosuccinimides, N-halopyridiniums, dihalides or transition metal halides (CuX_2 for instance).[7] These reagents, despite their undisputable synthetic usefulness, suffer from several limitations that include their cost and relatively low atom-economic aspect (see their range of molecular weight, MW, Scheme 1, top).

In addition to the amount of waste generated, a critical limitation of this electrophilic reagent synthetic approach is that concurrent non-catalysed electrophilic aromatic substitution occurs in many instance.[8,9] This is favored by the presence of activating substituent on the heteroaromatic substrates. Thus, such a competition with the targeted regioselective metal catalysed C–H activation is detrimental to atom-economy.

With the view to decrease undesired side-reactions, and the total cost of the transformation, the employment of widely available, intrinsically less reactive, or more selective, halogen sources appears to be highly desirable. These may include alkali halide nucleophilic sources, if suitable general synthetic routes are established (Scheme 1, middle). Several groups pioneered an approach of "nucleophilic" C–H halogenation promoted by palladium catalysts with selected N-directing groups. In 2010, Xu et *al.* reported calcium halide CaX_2 reagents for the *o*-functionalization of pyrimidine derivatives with cupric trifluoroacetate as the oxidant (Scheme 1, bottom).[10] A selective monohalogenation was achieved using 6.0 to 8.0 equiv. of calcium bromide. In 2014, Chen et *al.* reported the *o*-halogenation of an aromatic in the presence of sodium halides NaX (X = I, Br, Cl) using benzylamine derivatives.[11] A mixture of NaX, $NaXO_3$ and $K_2S_2O_8$ was used for the introduction of the halide on benzylamine derivatives, albeit with a difficult control of regioselectivity when several halogenation sites were available. Most recently, Liang and co-workers reported the employment of phenyliodanediacetate (PIDA) as the oxidant in the presence of NaCl and NaI for the N-directed Pd-catalysed halogenation of benzothiadiazoles.[12] This useful and promising catalytic system was surprisingly found ineffective for C–H direct bromination, and ultimately N-bromosuccinimide (NBS) has to be used. In 2020, Jiao et *al.* reported the bromination of pyridine and pyrimidine aryls in the presence of HBr as the nucleophilic halide with DMSO, which played the role of solvent and oxidant.[13] Additionally, few works on the nucleophilic C–H halogenation that are promoted by Cu, Ni or Rh were also reported.[14] Therefore, the generalization of these approaches to a larger range of useful directing-groups, and achieved from cheap and widely available nucleophiles is highly desirable.

We now report the conditions for a wide scope palladium-catalysed N-directed *o*-halogenation of heteroaromatics based on simple alkali metal halides as "nucleophilic" sources, using PIDA as the oxidant (Scheme 1, bottom). In this generalized protocol, the heteroaromatic substrates suitable for direct C–H halogenation are functionalized pyridines, pyrimidines, pyrazoles, oxazolines, naphtho[1,2-*d*]thiazoles, azobenzenes, and notably the selectivity-challenging and clickable/bioconjugable nitrogen-rich *s*-aryltetrazine. These substrates including N-directing groups were successfully employed for highly selective monohalogenation (X = I, Br and Cl) using the full range of alkali metals Li, Na, K and Cs. A good tolerance to substituents on the C–H-halogenated aryl was probed and the use of microwave conditions efficiently reduced long-time synthesis to less than one hour.

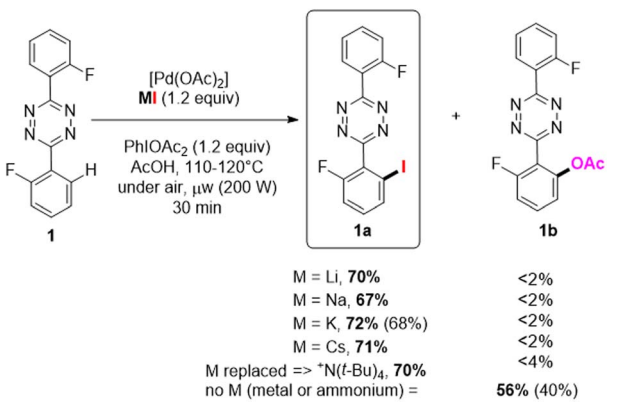
Results and discussion

N-directed palladium catalysed nucleophilic iodination of heteroaromatics

S-aryltetrazine were arguably the most challenging substrates for selective monohalogenation. The substrates can undergo up to four concurrent C–H functionalization reactions, and we previously disclosed its practical and very efficient *o*-C–H-fluorination, as well as multistep analogous halogenation using electrophilic reagents.[15–17] We envisioned, however, some room for improvement in terms of reagents and selectivity.

For the direct C–H iodination of 3,6-bis(2- fluorophenyl)-1,2,4,5-tetrazine **1** (Scheme 2) we explored the performances of various palladium-based catalysts, the full set of MI alkali halides as source (where M = Li, Na, K and Cs), and the oxidizing agents PIDA, PIFA, and $K_2S_2O_8$ within various solvents (see also Table S1 in ESI†). N-directed C–H bond activation was best achieved in the presence of $[Pd(OAc)_2]$ and PIDA, in acetic acid at 110 °C for 30 min under microwave conditions (μw, 200 W). All the alkali metal sources LiI, NaI, KI, CsI, and even N(*t*-Bu)$_4$I, were found compatible with the *s*-aryltetrazine substrate for its C–H iodination in excellent conversion up to 72% (Scheme 2), with the formation of *ca* 15–25% of the dihalogenated product. Overall, as fairly good selectivity is achieved for the monoiodinated product **1a** (67 to 72%), especially concerning the concurrent reaction of C–H acetoxylation that is found deleterious when electrophilic sources are used for this reaction.[15]

The cheapest potassium iodide was selected as most suitable reagent. Notably, KI was neither used in the pioneering works above-mentioned as "nucleophilic" source of halide. This new monoiodination methodology was found superior to our previous results according its conversion, selectivity, and importantly for the purification procedure.



Scheme 2 *o*-C–H iodination palladium-catalysed with alkali halides or ammonium salt as nucleophilic reagents: LiI, NaI, KI, CsI, [N(*t*-Bu)$_4$]I.

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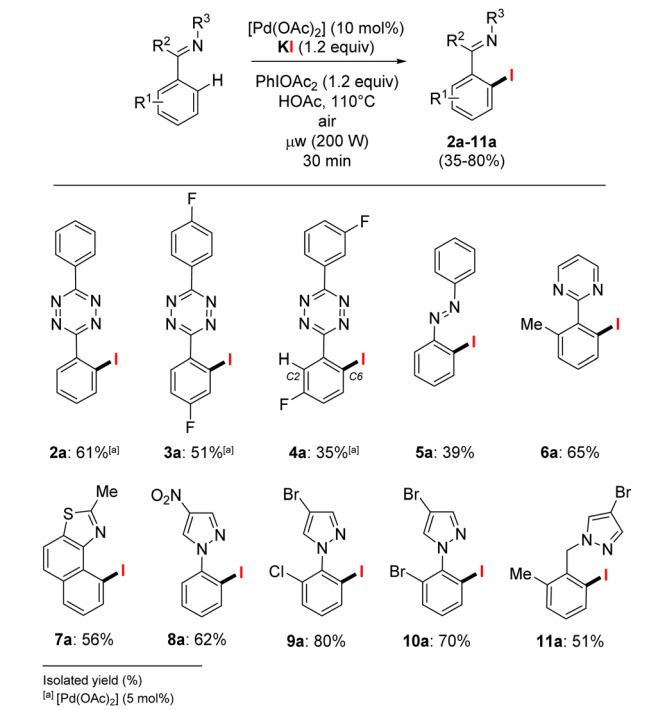
For instance, electrophilic reaction using NIS furnished 57% of **1a** due to a slightly better selectivity in favor of mono-functionalization observed with the "nucleophilic" C–H halogenation approach (typically, the use of 2 equiv. of NaI yielded **1a** and **1a′** in 67/33 ratio *vs.* 57/43 using NIS[16]). Without alkaline metal halide present the acetoxylated product **1b** was preferentially formed, and could be isolated in 40% yield (Scheme 2).

With these optimized conditions in hands, we further investigated the scope of heteroaromatic compounds as coupling partners in the C–H iodination reaction (Scheme 3).[15,16] We mainly achieved *o*-C–H monoiodination of *s*-aryltetrazines and azobenzene **1–5** (optimization details in Table S1 in ESI†). These substrates are arguably the most challenging substrates for selective monohalogenation since up to four concurrent C–H functionalization reactions may potentially occur. Pleasingly, alkali salts, which had neither been used before for such substrates (*s*-aryltetrazines), are clearly suitable halogen sources. Overall, the monoiodination was achieved in moderate to good isolated yields of 61% and 51% for **2a** and **3a** respectively. C3-substituted *s*-aryltetrazines are also suitable for C–H halogenation, the functionalization occurred in the *para*-position from the C3 group. Only traces of the C2-iodinated product was detected and the targeted C6-halogenated tetrazine **4a** was obtained in 35% isolated yield with satisfying purity (+99%). The presence of functional groups at the *meta*-position (C3) of the arene induces a dominant selectivity for the functionalization at C6, presumably the concurrent C2-position is sterically disfavoured since this effect is observed both for electron-donating or electron-withdrawing groups at C3, as previously reported by our group and others.[6a,8,18] Using a wider scope of heteroaromatic substrates, only minor reactivity changes were observed. [$Pd(OAc)_2$] at 10 mol% was found to be necessary for the conversion of azobenzene **5**, giving **5a** in 39% isolated yield. The aryl-pyrimidine **6**, with a six-membered ring directing group, achieved the aryl C–H *o*-iodination to give the pure **6a** in 65% yield.

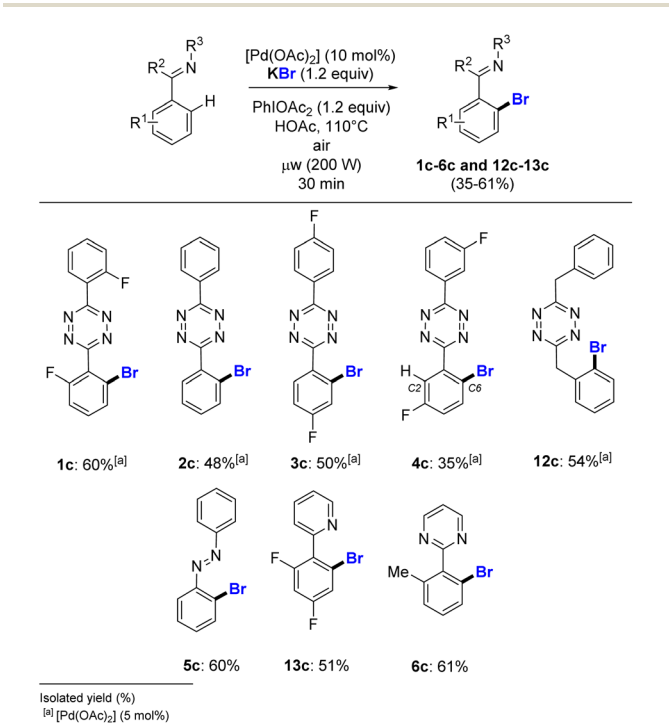
The other substrates with five-membered N-directing groups also achieved C–H *o*-iodination in satisfactory to good yields. The naphtho[1,2-*d*]thiazole **7** was successfully *o*-iodinated for **7a** in 56% isolated yield after side-products removal, including compounds from sp^3C–H iodination of the methyl group. The *o*-iodinated arylpyrazoles **8a** to **10a** were obtained in isolated yields above 60% and tolerated bromo and nitro functions, and **11a** with a remote directing bromopyrazole was isolated in 51% yield. Overall, the conversion of these various heteroaromatics is mostly achieved between 70–90% yields, with the formation of less than 15% of dihalogenated product (see Table S1 in ESI†). Accordingly, the need for separation with a high final purity led to isolated yields of **2a–11a** between 35 and 80%.

N-directed palladium catalysed bromination of heteroaromatics

Liang and co-workers reported a lack of reactivity of NaBr in the N-directed palladium catalysed *o*-bromination of benzothiadiazole derivatives.[12] We investigated the use of KBr as the halide source on various heteroaromatic substrates (Scheme 4). Under our conditions, the challenging bromination of *s*-aryltetrazines **1–4** was achieved, with good to moderate yields obtained for **1c–4c** in 60% to 35% isolated yields. This method also proceeded properly for the *o*-halogenation of 3,6-bis(benzylic) *s*-



Scheme 3 *o*-C–H iodination of heteroaromatics from KI halogen source.



Scheme 4 *o*-C–H bromination of heteroaromatics from KBr halogen source.

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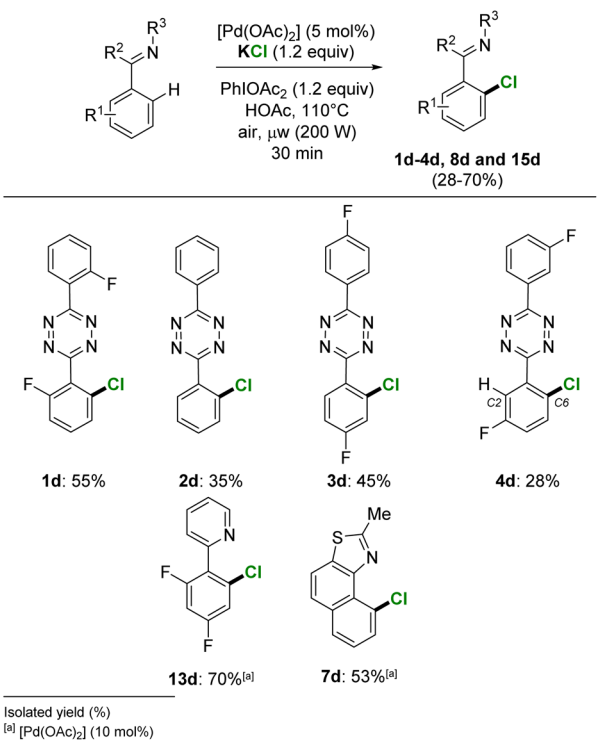
tetrazine **12**, giving pure **12c** in 54% yield. The azobenzene **5** gave 60% of brominated **5c**, a much higher yield than obtained for its iodinated counterpart **5a** (39%, Scheme 3). The pyridine and pyrimidine heteroaromatic substrates, which are in general broadly employed in C–H halogenation, were also successfully brominated in 51% and 61% isolated yield for **13c** and **6c**, respectively. This is valuable, since conversely for the catalysed C–H functionalization of 2,4-difluorophenyl pyridine in the presence of KI, the homocoupling reaction was achieved instead of the expected halogenation.[19]

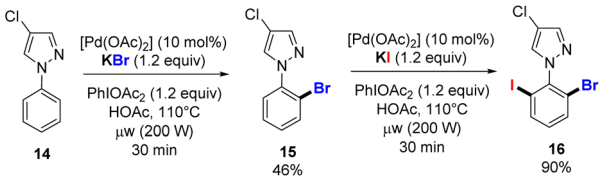
N-directed palladium catalysed chlorination of heteroaromatics

The palladium catalysed *ortho*-halogenation with nucleophilic alkali halides was further extended to chlorination. The selective *o*-C–H-monochlorination was achieved on a set of heteroaromatic substrates from the use of 1.2 equivalent of the low-mass KCl (MW = 74.6 g mol^{-1}). By using a reduced amount of palladium catalyst, [Pd(OAc)$_2$] 5 mol%, the *s*-tetrazines **1–4** were chlorinated to give isolated yields of pure **1d–4d**, in 55%, 35%, 45% and 28% yield, respectively (Scheme 5). The 2,4-difluorophenyl pyridine and naphtho[1,2-*d*]thiazole substrates also successfully achieved a selective *o*-aryl monochlorination, giving 70% and 53% isolated yields for **13d** and **7d**, respectively.

Remarkably, the full range of alkali metals Li, Na, K and Cs with the various halides displayed very similar reactivity. While in-depth mechanistic investigation is out of the scope of the present study, we hypothesize that classical Pd(II)/Pd(IV) process may occur, with the possible formation of PhI(X)$_2$ or PhI(X)(OAc) as "genuine" halogenation reagents by ligand exchange with OAc (X = I, Br and Cl). This would be consistent with the apparent unicity of reactivity. Experimental and computational reports are available concerning ligand exchanges between salts and hypervalent iodine, and the related radical (non-electrophilic) reactivity.[20]



Scheme 5 *o*-C–H chlorination of heteroaromatics from KCl halogen source.



Scheme 6 Sequential palladium-catalysed *o*-C–H halogenation.

Finally, we used our new alkali halide-based C–H functionalization protocol to access the unsymmetrical trihalogenated pyrazole **16**, starting from the phenyl 4-chloropyrazole **14** and by sequential C–H bond activation (Scheme 6). The first halogenation takes place in the presence of 10 mol% of [Pd(OAc)$_2$], KBr (1.2 equiv.), PIDA (1.2 equiv.) in HOAc at 110 °C for 30 min under microwave irradiation. The mono *o*-brominated pyrazole **15** was obtained in 46% isolated yield, which allowed the second functionalization under similar conditions using KI instead of KBr and a high yield for **16** was obtained without any other byproduct formed.

Conclusion

We reported a novel convenient protocol for a palladium-catalysed N-directed *o*-halogenation of heteroaromatic based on the use of simple alkali metal halides as nucleophilic sources and PIDA as oxidant. Monofunctionalization is achieved in majority, in general together with the formation of *ca* 15–25% of the dihalogenated product.

The reaction was found suitable for a large range of structurally different N-heteroaromatic substrates, which includes pyridines, pyrimidines, pyrazoles, oxazolines, naphtho[1,2-*d*] thiazoles, azobenzenes, and specifically the topical (in click chemistry and bioconjugation applications[15,16]) and challenging nitrogen-rich heteroaromatic *s*-tetrazine. Highly selective *o*-aryl monohalogenation was achieved (halogen = I, Br and Cl), which compared favorably to the classical protocols using electrophilic reagents in palladium-catalysed N-directed *ortho*-C–H halogenation. These results paved the way for the use of simple alkali halides in both inexpensive (cheaper salts) and more atom-economic (mass economy) conditions for selective palladium-catalysed C–H halogenation.

Authors and distributions

A. D. and O. A. performed the experiments, and J. R. and J.-C. H. conceived the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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