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Palau'chlor: A Practical and Reactive Chlorinating Reagent

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Supporting Information

ABSTRACT: Unlike its other halogen atom siblings, the utility of chlorinated arenes and (hetero)arenes are twofold: they are useful in tuning electronic structure as well as acting as points for diversification via cross-coupling. Herein we report the invention of a new guanidine-based chlorinating reagent, CBMG or "Palau'-chlor", inspired by a key chlorospirocyclization en route to pyrrole imidazole alkaloids. This direct, mild, operationally simple, and safe chlorinating method is compatible with a range of nitrogen-containing heterocycles as well as select classes of arenes, conjugated π-systems, sulfonamides, and silyl enol ethers. Comparisons with other known chlorinating reagents revealed CBMG to be the premier reagent.

Unlike other aromatic halides, aryl chlorides have a dichotomous function in the areas of pharmaceuticals (e.g., Plavix, Abilify, Lunesta),[1−3] imaging (^{11}C-raclopride),[4] natural products (vancomycin, aureomycin),[5,6] agrochemicals (DDT, Dicofol),[7] and materials science (Cl_8-PTCDI, Cl_{16}-CuPc).[8] Their presence confers molecules with both *function* and *functionalizability*. Within the agrochemical and drug discovery arenas, chlorination is usually motivated by a desire to enhance biological properties in a similar vein to fluorination (but in contrast to bromination or iodination). However, aryl chlorides stand alone in their nearly limitless potential for diversification using cross-coupling chemistry (like bromine and iodine but in stark contrast to fluorine). In view of the widespread presence of aryl chlorides, it is somewhat puzzling that modern methods for direct chlorination still rely on age-old reagents. In this communication, the invention of a new guanidine-based reagent for the direct electrophilic chlorination of heteroaromatic systems is reported. This reagent is highly reactive and stable and can accomplish C−H chlorinations that conventional reagents fail to achieve under identical conditions.

Direct methods for aromatic C−H chlorination can be classified into three main modes (Figure 1A), some of which present drawbacks: (1) electrophilic aromatic substitution (S_EAr),[9,12−19] where reagents can be too reactive, unselective, or, conversely, unreactive without the presence of strong electron-donating groups on the aromatic system; (2) hydrogen−metal exchange (specifically, directed ortho metalation) followed by trapping with a Cl^+ source,[10] which can be efficient and regioselective but requires the use of a strong base and a directing group; (3) transition-metal-catalyzed C−H activation

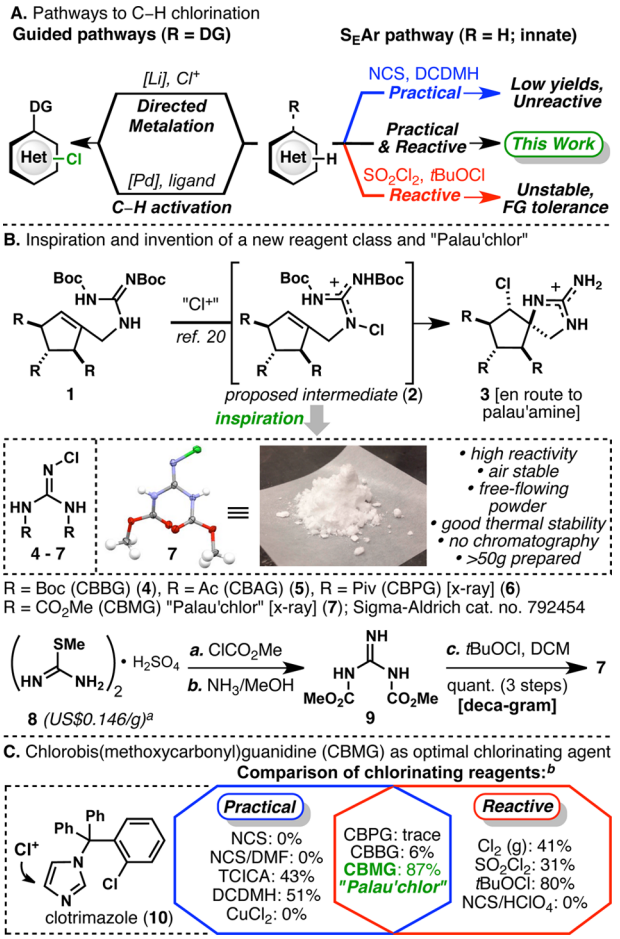

Figure 1. Invention of CBMG ("Palau'chlor") inspired by the pyrrole imidazole alkaloid family of natural products. Notes: [a]Starting material comparable in cost to the NCS precursor (succinimide = US $0.144/g from Aldrich). [b]Additional data on imidazo[1,2-*a*]pyrazine are included in the Supporting Information (SI).

methods, which are emerging as useful tools with regioselectivity that is often complementary to classical methods, though the substrate scope can be limited.[11]

Innate C−H chlorination (S_EAr) is perhaps the oldest method to prepare aromatic chlorides and can be generalized into two main classes: reactive and practical. Reactive S_EAr methods

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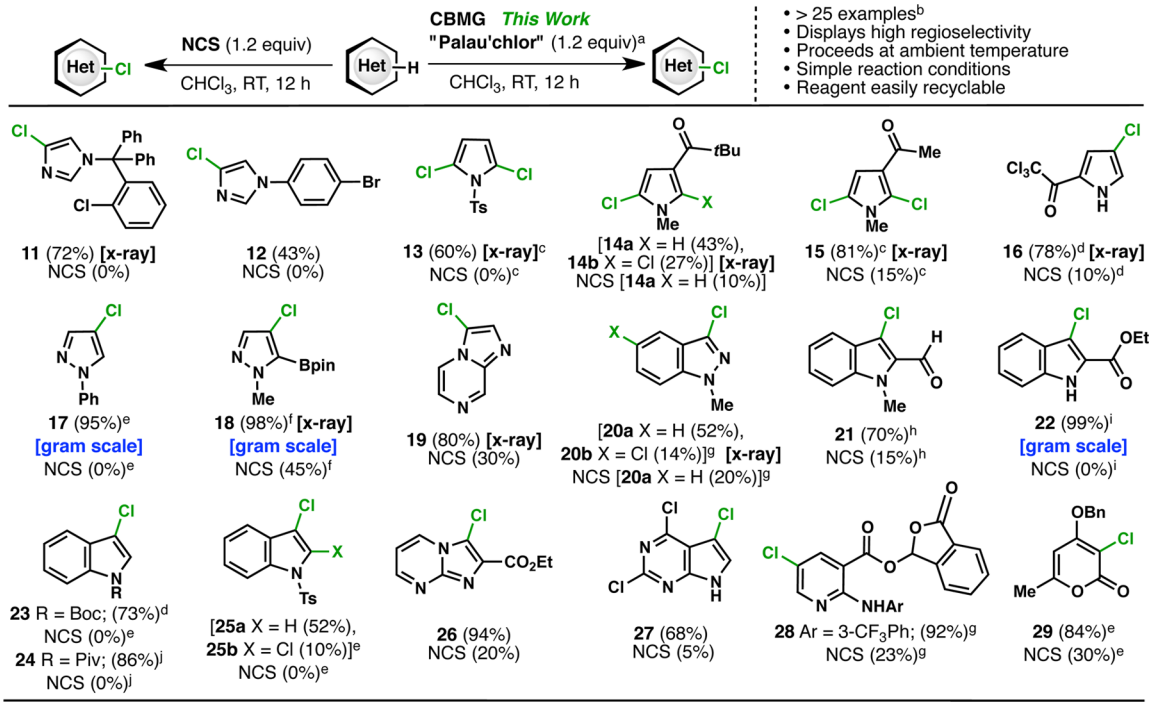
Table 1. Scope of C−H Chlorination of Heteroarene Substrates



[a]Conditions: heterocycle (1.0 equiv), NCS or CBMG (1.2 equiv), $CHCl_3$ (0.1 M). Isolated yields are shown. [b]Decomposition observed with most aldehydes. [c]CBMG (2.2 equiv). [d]CBMG (2.2 equiv), 50 °C, 1 h. [e]CH_3CN. [f]Product could be purified only by filtration (NCS crude reaction shown as ^{1}H NMR yield). [g]CH_3CN, CBMG (2.2 equiv); nonactivated pyridines, 2-hydroxypridine, and 2-(*tert*-butoxy)pyridine were not reactive substrates under these conditions. [h]30 min (NCS at 12 h = 52%). [i]Product was unstable. [j]1-Acetylindole was chlorinated by CBMG and NCS in lower yields (28% and 3%, respectively).

utilize some of the most traditional chlorinating reagents (Cl_2 or SO_2Cl_2), which generally have safety liabilities that limit their application because of their aggressive reactivity.[12] Mild methods use substantially less reactive reagents [*N*-chlorosuccinimide (NCS) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH)]. While these reagents (e.g., NCS) are inexpensive, easy to handle, and therefore practical, their reduced reactivity can limit their application.[13,14] Often operating with radical-based mechanisms, *t*BuOCl serves as a valuable chlorinating reagent,[15] but its reactivity is variable on arenes[16] and it is dangerously light-sensitive (releases MeCl),[15] heat-sensitive (releases Cl_2),[17] and moisture-sensitive (ignition).[18] Other chlorinating reagents exist,[19] but many of these are toxic (e.g., PhSeCl,[19a]), explosive (e.g., $TiCl_4/CF_3CO_3H$[19b]), hygroscopic (e.g., NCS/$ZrCl_4$[19c]), or strongly acidic (e.g., $SbCl_5$,[19d] *N*-chloramines in neat acids[19e]); hence, many chlorination reagents and methods have significant liabilities that limit their application in organic chemistry.

During a study of the mechanism of the intramolecular chlorospirocyclization of **1** to **3** (Figure 1B),[20] it was discovered that a stable and hitherto unisolated *N*-chloroguanidine, **2**, was the functioning chlorinating agent. This finding inspired broad exploration into reagents of similar structure, such as **4**−**7**, which could function as potentially powerful chlorinating reagents. *A particularly promising gauge of the chlorinating ability of these new reagents was the observation that benzenesulfonamide was N-chlorinated in quantitative yield whereas tBuOCl or NCS failed to deliver any product (vide infra).*

With a focus on heteroaromatic chlorination, clotrimazole (**10**) emerged as an ideal model substrate for comparing the reactivities of chlorinating agents, since NCS failed to deliver any chlorinated product at room temperature (rt). Systematic variation of the pendant acyl groups on the guanidine led to the identification of chlorobis(methoxycarbonyl)guanidine (**7**, CBMG, "Palau'chlor") as the optimal chloroguanidine reagent. Subsequent analysis has shown CBMG to be an air-stable, bench-stable, free-flowing powder. Initial assessment of the thermal stability of CBMG by differential scanning calorimetry (DSC) showed no thermal events below 100 °C, with a calculated adiabatic decomposition temperature over 24 h (ADT24) of >80 °C and a projected stability of greater than 1 year at rt (at 25 °C under isothermal conditions).

We were interested in seeing how this first-in-class reagent compared to existing chlorinating reagents, and thus, we screened a range of chlorinating agents and compared their reactivities with **10** to that of CBMG (Figure 1C). The results of our studies indicated that CBMG furnishes a higher yield of product than Cl_2, SO_2Cl_2, and *t*BuOCl while being as cost-effective as NCS. CBMG can be generated in large quantities and has now been commercialized through Sigma-Aldrich (CBMG, Palau'chlor, cat. no. 792454).

With this new chloroguanidine reagent in hand, the scope of heteroarene C−H chlorination was evaluated (Table 1). Numerous substrates showed unmatched reactivity with CBMG compared with NCS under identical conditions (1.2 equiv of chlorinating reagent). Although CBMG showed slightly better solubility in $CHCl_3$ at rt compared with NCS, its performance was higher regardless of the solvent employed.[21] Thus, imidazoles (**11**, **12**), pyrroles (**13**−**16**), pyrazoles (**17**, **18**), indoles (**21**−**25**), and other heterocycles (**19**, **20**, **26**−**29**) could all be cleanly chlorinated.

In most cases, substrates with multiple potential reaction sites exhibited high levels of regioselectivity, producing a single

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isomer. In cases where a single regiosiomer was not produced, bis-C−H chlorination was often observed (**13**−**15**, **20**, **25**). 2-(Trichloroacetyl)pyrrole can be used as a versatile synthetic intermediate to access either 4- or 5-functionalized pyrrole-2-carboxamides.[22] Most likely because of poor selectivity (over-chlorination and potential polymerization using SO_2Cl_2),[23] the commercial availability of **16** is limited (Ryan Scientific Inc.; US $390/g). Under the standard conditions, CBMG proved to be a selective reagent, providing **16** in good yield. A key feature of CBMG is the ease of post-reaction purification, leading to efficient reagent recycling.[24]

An investigation of the reaction rate was conducted using two heteroarene substrates (Figure 2). Imidazo[1,2-*a*]pyrazine

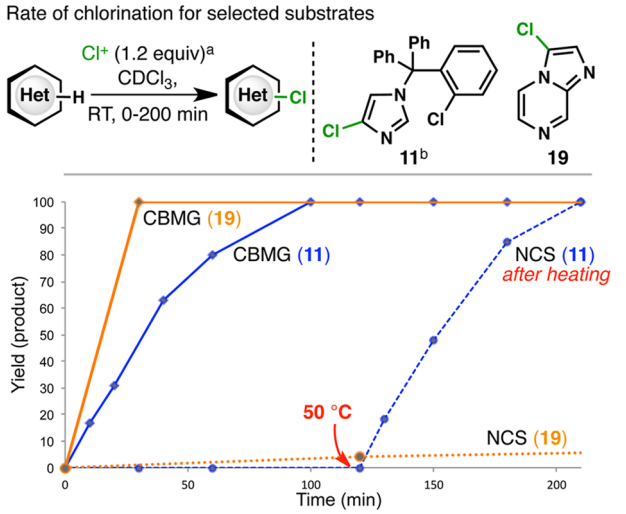


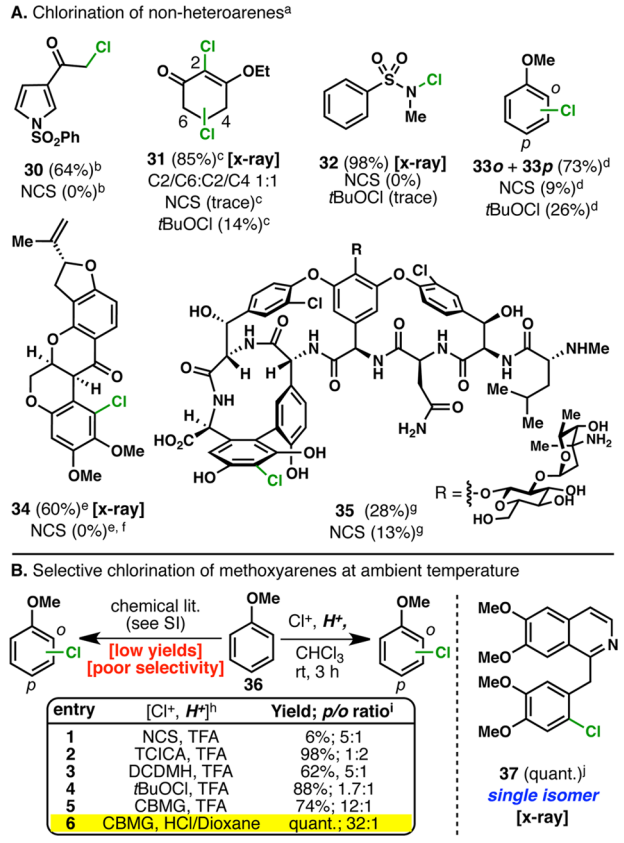
Figure 2. Reaction rate and mechanistic study. Notes: [a]The standard conditions were employed using CBMG or NCS (1.2 equiv); yields were recorded as ^{1}H NMR yields using 1,2-dichloroethane as an internal standard. [b]The clotrimazole reaction was heated to 50 °C after it showed no reactivity at rt.

(precursor to **19**) and clotrimazole (**10**) are substrates that show a representative contrast between CBMG and NCS. For **10**, reaction with CBMG at rt gave a quantitative yield (^{1}H NMR) after 100 min, whereas NCS was completely unreactive at rt. NCS reacted with **10** only after the reaction mixture was heated to 50 °C. Similarly, imidazo[1,2-*a*]pyrazine reacted with CBMG to give a quantitative yield (^{1}H NMR) after 40 min at rt, but only trace amounts had reacted with NCS after 40 min. It is worth noting that the increased reactivity of NCS upon heating is not sufficient to mimic the performance of CBMG, and in some instances (e.g., **31**) only trace chlorinated product was observed after heating for a prolonged period.

To understand the mechanistic differences between CBMG and NCS, the kinetic isotope effects (KIEs) were determined in the reactions of anisole (**36**) and d_8-**36** with CBMG versus NCS (see the SI). When **36** and d_8-**36** were monitored using GC, the rates of chlorination with CBMG showed a normal KIE of 1.2, which is only slightly greater than unity. This indicates that the aromatic C−H bond is not likely to be broken in the rate-determining step (RDS) (typical of S_EAr). This is supported by the fact that CBMG and NCS show identical KIEs of 1.2 on **36** and d_8-**36**, wherein NCS has been previously shown to operate by an S_EAr mechanism with dearomatization as the RDS.

In addition to the heteroarene substrates listed in Table 1, other organic substrates also displayed improved reactivity using

Table 2. Chlorination of Non-Heteroarenes (Isolated Yields Are Shown)



[a]Phenylsilane showed no reactivity toward CBMG at rt; chlorodeboronation of 3-nitrophenylboronic acid gave no apparent difference in yield compared with ref 32. [b]One-pot operation: TMSOTf (3.0 equiv), DIPEA (3.0 equiv), CH_2Cl_2, then CBMG or NCS (1.5 equiv). [c]Inseparable mixture of regioisomers. [d]GC yield after 12 h at 60 °C. [e]CBMG or NCS (2.2 equiv). [f](NCS at 50 °C, 12 h = 26%). [g]CBMG or NCS (2.0 equiv), DMF, rt, 48 h, preparative HPLC purification. [h]Chlorinating reagent (1.0 equiv), H^+ (1.0 equiv). [i]^{1}H NMR yields using CH_3NO_2 as an internal standard. [j]Isolated yield after preparative HPLC.

the described process with CBMG compared with NCS and *t*BuOCl (Table 2). Chemoselective *α*-chlorination of a carbonyl compound was achieved from the corresponding silyl enol ether in a one-pot operation. Electron-rich conjugated *π*-systems and sulfonamides were also competent substrates for direct C−H and N−H chlorination. In view of the fact that CBMG is prepared from *t*BuOCl and the similar *N*-chlorinated sulfonamide Chloramine-T is prepared from in situ-generated NaOCl (from NaOH and Cl_2),[25] it is somewhat puzzling that neither benzenesulfonamide nor *N*-methylbenzenesulfonamide was effectively chlorinated with either NCS or *t*BuOCl alone under identical conditions.[26]

Furthermore, CBMG can be used in a complex setting. For example, rotenone (a common pesticide)[27] was selectively chlorinated in the presence of an olefin to give **34**.[28] In an even more extreme case of functional group tolerance, exposure of vancomycin to the reaction conditions in *N*,*N*-dimethylformamide (DMF) showed a 2-fold increase in C−H chlorination of the electron-rich biaryl relative to NCS.[29]

After an extensive survey and attempted reproduction of literature procedures,[30] it was determined that regioselective

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chlorination (for landmark examples of regioselective bromination, see ref 29) of simple arenes remains an area in need of improved technology, and CBMG may also benefit this area of study. Although CBMG was found to react with anisole (**36**) at elevated temperatures (Table 2A), it was also found that the addition of 1.0 equiv of Brønsted acid significantly accelerates the reaction.[31] Thus, treatment of **36** with 1.0 equiv of CBMG and 1.0 equiv of trifluoroacetic acid (TFA) led to a 74% yield of products with a remarkable 12:1 *para:ortho* selectivity (surpassing all selectivities known).[30] Furthermore, this reagent was compared with a host of other chlorinating agents, which demonstrated that CBMG/TFA is superior in regioselectivity (Table 2B, entries 1−5). This dramatic effect was accentuated when the acid was changed from TFA to HCl (1.0 equiv), where a quantitative yield was obtained with 32:1 para:ortho selectivity (Table 2B, entry 6). To showcase the ability of CBMG to perform as a selective chlorinating reagent, Pavabid was subjected to the CBMG protocol to give **37** as a single product (Table 2B).

In summary, a first-in-class guanidine-based chlorinating reagent (**7**, CBMG, "Palau'chlor") was invented by studying the mechanism of a key chlorospirocyclization en route to palau'amine. CBMG is comparable in both cost (raw materials and high synthetic efficiency) and molecular weight to the classic reagent NCS yet exhibits a reactivity profile that is equivalent to or better than those of more aggressive reagents (SO_2Cl_2, Cl_2, *t*BuOCl) without sacrificing functional group tolerance. This reactive yet practical reagent has been shown to outperform a plethora of known chlorinating systems across a wide range of substrate classes, leading to its commercialization by Sigma-Aldrich. The dichotomous function and widespread use of (hetero)aryl chlorides bodes well for the use of **7** in many important branches of chemical science. The general use of guanidine-based reagents in the electrophilic transfer of other atoms (I, Br, F, Se, S, etc.) and in asymmetric synthesis are subjects worthy of additional study.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, KIE complete data acquisition, DSC analysis, and analytical data for all new compounds, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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