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Deaminative chlorination of aminoheterocycles

Clément Ghiazza, Teresa Faber, Alejandro Gómez-Palomino and Josep Cornella ✉

Selective modification of heteroatom-containing aromatic structures is in high demand as it permits rapid evaluation of molecular complexity in advanced intermediates. Inspired by the selectivity of deaminases in nature, herein we present a simple methodology that enables the NH₂ groups in aminoheterocycles to be conceived as masked modification handles. With the aid of a simple pyrylium reagent and a cheap chloride source, $C(sp^2)$–NH₂ can be converted into $C(sp^2)$–Cl bonds. The method is characterized by its wide functional group tolerance and substrate scope, allowing the modification of >20 different classes of heteroaromatic motifs (five- and six-membered heterocycles), bearing numerous sensitive motifs. The facile conversion of NH₂ into Cl in a late-stage fashion enables practitioners to apply Sandmeyer- and Vilsmeier-type transforms without the burden of explosive and unsafe diazonium salts, stoichiometric transition metals or highly oxidizing and unselective chlorinating agents.

nstallation and removal of chemical functionalities in complex molecular settings with a high degree of precision still remain a challenging and highly coveted milestone for organic chemists, as they would permit facile decoration of any molecular entity at will[1,2]. Nature offers a clear example of this strategy and has mastered an intricate system of enzymatic biochemical processes to enable the selective modification of specific groups in large chemical systems. A notable example is the conversion of cytidine to uridine via a deaminative process: aided by a Zn ion in the active site, these enzymes replace the NH₂ with a molecule of H₂O (Fig. 1a)[3,4]. From the chemical point of view, the cleavage of a $C(sp^2)$-N bond is energetically costly (bond dissociation energy, $102.6 \pm 1.0 \, \text{kcal mol}^{-1}$) and amido groups are extremely poor leaving groups (NH₂⁻), with virtually no examples in the synthetic world[5]. Yet, deaminases overcome these hurdles and enable the process to occur with high efficiency at room temperature. Inspired by this selective deamination process, we hypothesized that a synthetic tool that enables the precise removal of $C(sp^2)$-NH₂ groups in various complex heterocyclic frameworks beyond nucleobases would be highly desirable. Aminoheterocycles are at the core of many biologically relevant compounds such as fungicides, herbicides, pharmaceutical compounds, natural products, vitamins, DNA, RNA and so on (Fig. 1b)[6–8]. Hence, the conversion of the NH₂ group into a modular and versatile leaving group would be highly desirable. In this sense, we turned our attention to heteroaryl chlorides since they have occupied a preferential place in synthetic routes due to the myriad of robust methods available for their chemical modification[9].

The classical Sandmeyer reaction remains the 'textbook' reaction when the conversion of $C(sp^2)$-NH₂ into $C(sp^2)$-Cl is desired. Yet, it still relies on the diazotization of the amine followed by chlorination with CuCl (Fig. 1c, left)[10,11]. This protocol has been useful in simple anilines and certain aminoheterocycles. However, the strongly oxidizing and acidic conditions needed to reveal the diazonium salt present a certain incompatibility for structures containing more sensitive functionalities. More importantly, the formation of nitrogen-rich heteroaryl diazonium salts results in highly energetic compounds, which raise severe concerns about their safe handling[12,13]. Recently, awareness has also been raised by the use of aqueous nitrite solutions, which can lead to important levels of carcinogenic N-nitrosamines[14]. Altogether, these setbacks prohibited the translation of such a strategy in complex settings, and the perception of $C(sp^2)$-NH₂ as late-stage functionalization

handles was abandoned. With the aim of providing a robust protocol for $C(sp^2)$-Cl bond formation, we drew inspiration from the venerable Vilsmeier-type reaction that converts amides into imidoyl chlorides (Fig. 1c, right). This powerful transformation has found notorious applications in organic synthesis; yet, the use of highly reactive and unselective POCl₃ relegates this disconnection to the early stages of the synthesis, making it incompatible with late-stage modifications[15,16].

Herein, we present a method that merges the availability of starting materials offered by the Sandmeyer approach with the usefulness of the heteroaryl halides obtained when a Vilsmeier-type disconnection is desired. The method smoothly converts NH₂ groups from heteroaromatic compounds into heteroaryl chlorides by means of a simple and commercially available pyrylium reagent (Pyry-BF₄, 1)[17] and various chloride sources (Fig. 1d). The method is demonstrated to be applicable to >20 distinct types of heterocyclic motifs, including both five- and six-membered rings containing N, O and S atoms. Importantly, the protocol is characterized by the broad functional group tolerance, thus permitting the formation of electrophilic $C(sp^2)$-Cl bonds onto complex pharmaceuticals, agrochemicals and natural products in a late-stage fashion. To contextualize the functional group tolerance of the reported methodology, we benchmarked our system with the state-of-the-art Sandmeyer conditions, demonstrating that our protocol is truly enabling in providing the heteroaryl chloride. Finally, we show that this reactivity is not limited to chloride anions, and we demonstrate that bromide as well as fluoride can also deliver the halogenated product.

Results and discussion
Our investigations started with an interesting behaviour observed for the Zincke salt in solution. When 1-chloro-2,4-dinitrobenzene (2) is refluxed in the presence of pyridine (3), the Zincke salt precipitates in quantitative yields (4) and is easily separated and purified by filtration (Fig. 2a)[18]. Yet, when 4 is dissolved in MeCN, partial formation of 2 and 3 was observed in a 1:1 ratio, suggesting a reversible process. Increasing the temperature and diluting the solution led to the almost quantitative recovery of the 1-chloro-2,4-dinitrobenzene (2) as well as pyridine (3). Despite the wealth of literature for the reaction of nucleophiles with the Zincke salt, the use of the chloride counterion as a nucleophile to recover the parent aryl chloride 2 remained largely underexplored[19]. Although a plethora of examples of nucleophilic aromatic substitution exist with Cl regarded as

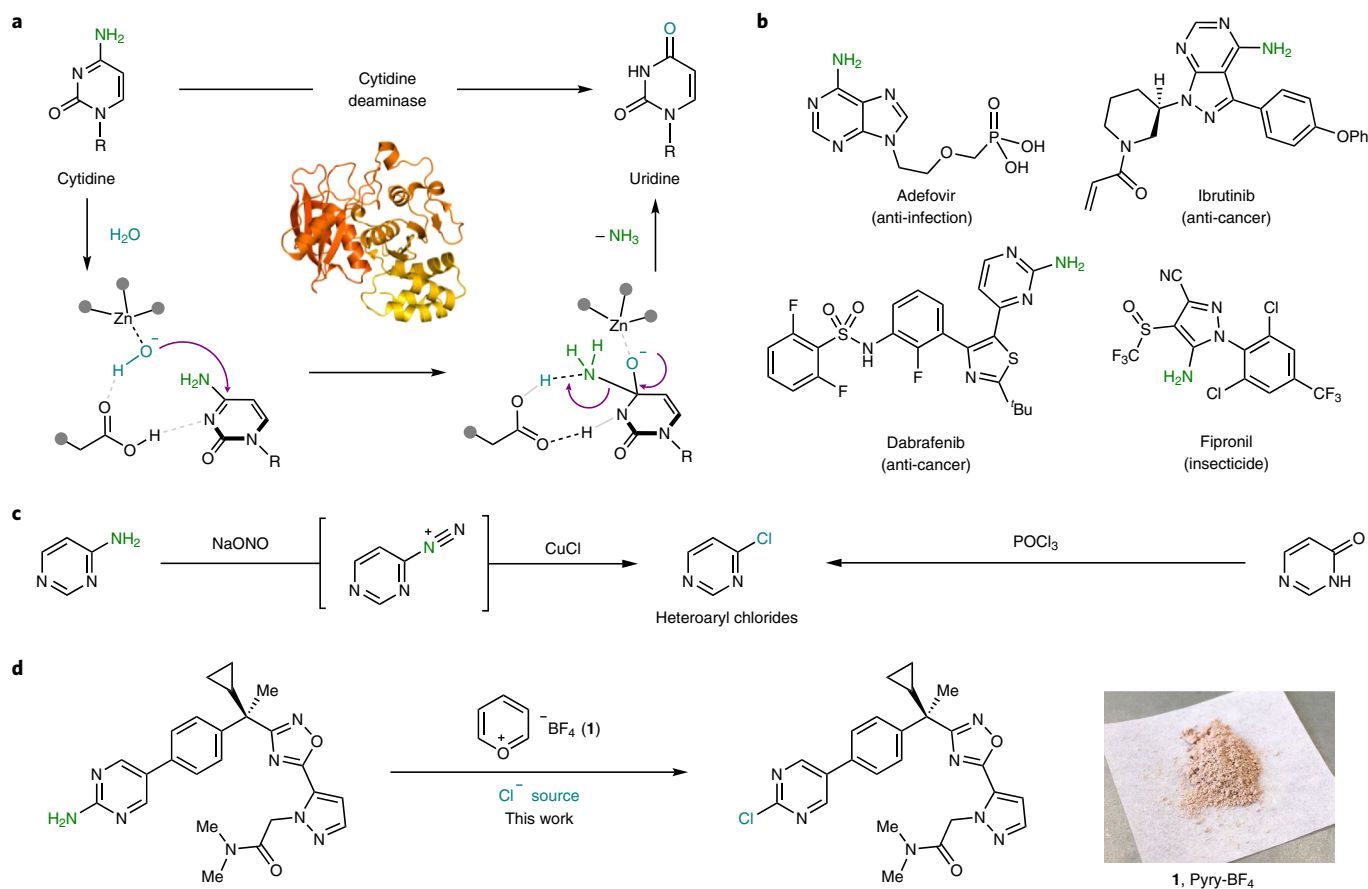Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany. ✉e-mail: cornella@kofo.mpg.de

Fig. 1 | Selective modification of NH₂ moieties, state of the art and challenges. a, Deaminases catalyse the conversion of cytidine to uridine using a mild and highly chemoselective exchange of NH₂ for an OH. Enzyme picture from Protein Data Bank no. 6K63 (ref. [32]). **b**, Compounds bearing the C(sp^2)–NH₂ group are ubiquitous in nature and are part of many biological compounds. **c**, The widely exploited Sandmeyer- and Vilsmeier-type reactions. Sandmeyer's limitations include explosive diazonium intermediates, limited functional group tolerance preventing its use for late-stage applications and being challenging for five-membered N-heterocycles. Vilsmeier-type reactions are relegated to early stages as they pose chemoselectivity issues, require high temperatures for five-membered rings and suffer from the low availability of the precursors. **d**, Chemoselective deaminative chlorination of aminoheterocycles using Pyry-BF₄ **1** is applicable to molecular systems bearing various heterocyclic frameworks bearing sensitive functional groups enabling the application of this strategy in late stages without any scalability issues.

the leaving group, reports on its role as nucleophile are comparatively much less exploited[20–23]. Inspired by these observations, we speculated that a similar behaviour could be translated to other arylpyridinium chloride systems, namely the product of oxidative dimerization of pyridine (**6**)[24]. Indeed, when compound **6** is heated in MeCN at 80 °C under diluted conditions (0.1 M), almost complete conversion to 4-chloropyridine (**7**) was observed with concomitant formation of pyridinium hydrochloride (**8**; Fig. 2b). This result immediately suggested that this phenomenon is not restricted to activated aryl moieties but also extends to heteroaromatic substrates. Our group has recently reported on the synthesis and properties of a simple pyrylium reagent (Pyry-BF₄, **1**) and its capacity to engage certain azines in Zincke-type reactivity[25–27]; although narrow in scope, the Pyry-BF₄ displayed high chemoselectivity for amino groups. Then, we envisaged that a merger of the reactivity observed in Fig. 2b in combination with the selectivity offered by Pyry-BF₄ would provide an opportunity for a broad and chemoselective deaminative chlorination strategy. To test this hypothesis, we subjected oxazole **9** to pyridinium formation with Pyry-BF₄ (**1**), which smoothly afforded pyridinium tetrafluoroborate **10** (Fig. 2c). At this point, various chloride sources were examined to effect an anion exchange and trigger the conversion of the C(sp^2)–N bond to a C(sp^2)–Cl bond (Fig. 2c, inset table). When using an etherated HCl solution, complete chlorination was obtained at room temperature

(Fig. 2c, entry 1, inset table). The use of a non-Brønsted acidic counterion such as MgCl₂ boded well and smoothly delivered **11** at 80 °C (Fig. 2c, entry 2, inset table). Noteworthily, 2.0 equivalents of trimethylsilyl chloride (TMSCl) quantitatively furnished the desired oxazolyl chloride **11** under milder conditions (Fig. 2c, entry 3, inset table). Anticipating potential issues when translating this methodology to complex molecules bearing acid-sensitive functionalities, we tested a chloride source bearing a non-coordinating cation. The use of 4.0 equivalents of ^{n}Bu₄NCl displaced the pyridine and forged **11** in excellent yields (Fig. 2c, entry 4, inset table). To provide facile and practical set-ups, a single-flask operation was established, which enables the formation of the pyridinium salt and subsequent in situ chlorination in high yields with no special precautions required (Fig. 2d). In order to increase the translational potential of the methodology, we demonstrated that alternative solvents with higher boiling points than MeCN such as benzonitrile, o-xylenes or propylene carbonate were also amenable for this one-pot sequence.

Having established a protocol using various chloride sources, we turned our attention to explore the scope of the aminoheterocycle (Table 1). First, we engaged a panel of 4- and 2-aminopyridines (**7**, **12–20**). Tuning the temperature turned out to be crucial to achieve satisfactory yields and accommodate functionalities such as halides (**12**, **14**), aromatic rings (**16**, **17**), an ester (**15**), a morpholine (**18**), a nitro (**19**) or a cyano (**20**). Diazines, including pyrimidine (**21**, **22**)
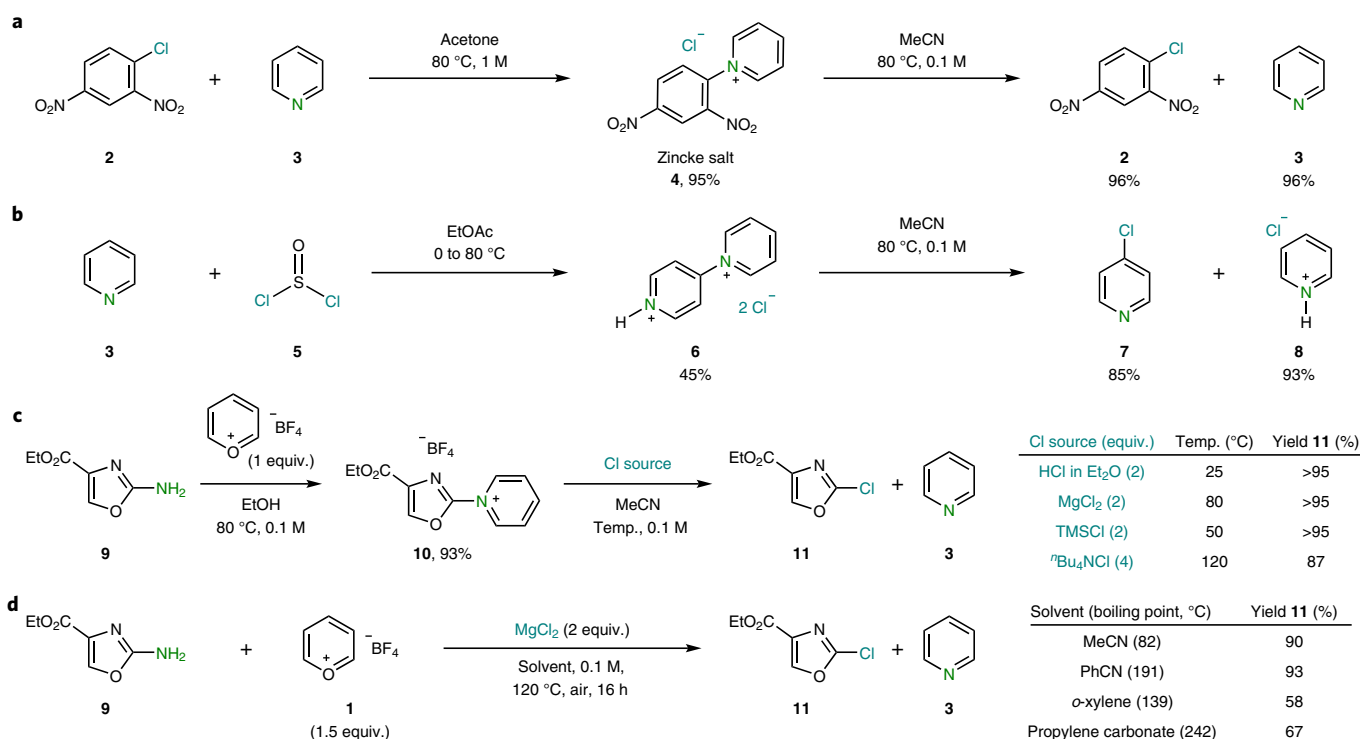
Fig. 2 | Deaminative chlorination: preliminary observations and optimized procedure. a, Interrupted Zincke reaction: the formation of pyridinium chloride is reversible depending on concentration and solvent. **b**, A similar behaviour to Zincke salts is observed for other heteroaromatic pyridinium chlorides. **c**, Development and implementation of a two-step deaminative chlorination of aminoheterocycles using various chloride sources and Pyry-BF$_4$. Temp., temperature. **d**, Conditions for an open-flask one-pot deaminative chlorination.

and pyridazine (**23**), were also smoothly converted to their chlorinated analogues in good yields. When our protocol was applied to herbicide chloridazone, high yields of the dichlorinated pyridazone **24** were obtained. Even the polyaromatic and crowded acrisorcin could be converted in 9-chloroacridine (**25**), albeit at 36%. Importantly, fused polycyclic substrates present at the core of biologically relevant molecules such as adenine or remdesivir, were smoothly converted to their chlorinated analogues in very good yields (**26** and **27**). Contrary to most strategies based on the Vilsmeier approach, our protocol boded well with five-membered heteroaromatic amines. For example, fused triazolopyridine, a motif present in certain sodium current inhibitors, smoothly afforded compound **28** in excellent yields[28]. Benzo-fused five-membered rings bearing other heteroatoms, such as benzothiazoles and isobenzothiazoles, which include drugs such as riluzole, boded well with the protocol obtaining excellent yields of the chlorinated analogues (**29–31**). Simple five-membered rings bearing sensitive functionalities such as ester or oximine were also well tolerated, as exemplified by **11** and **32**. To further study the functional group tolerance, a variety of oxazole-based compounds bearing pendant functionalities were scrutinized. The presence of halogens (Cl, I, Br, F), pyridine, cinnamyl, cyano, methylsulfone or even aldehyde posed no difficulties for chlorination (**33–40**). Heterocycles bearing three heteroatoms prone to ring-opening such as thiadiazole and oxadiazole (**41**, **42**) were smoothly chlorinated in high yields. The presence of a free secondary alcohol in **43** required the use of ^{n}Bu$_4$NCl to avoid side reactions through Mg-induced dehydration. Based on the functional group tolerance observed, we envisaged our protocol to be applicable to more complex and densely functionalized bioactive molecules. Gratifyingly, when the deaminative protocol was applied to hepatitis B pro-drug adefovir diethyl, analogue **44** was obtained in 57% yield. The anti-inflammatory amlexanox was successfully chlorinated at the two position of the pyridine motif (**45**).

Thiazole derivatives from amoxapine, paroxetine or SF$_5$-containing building blocks behaved well and were smoothly converted to the corresponding chloride in high yields (**46–48**). Remarkably, chlorination of the pyrimidine moiety in lipoxygenase-activating protein antagonist (BI-665915) was obtained in 38% yield (**49**), tolerating the presence of the rather weak N–O bond of oxadiazole, among others. Insecticide fipronil bearing a cyano and a trifluoromethylsulfoxide embedded in a pyrazolyl ring posed no difficulties for chlorination (**50**). Despite the presence of a Michael acceptor and a piperidinyl moiety, chlorination of the pyrazolopyrimidine core of anti-cancer ibrutinib smoothly occurred in 87% yield (**51**). Benzothiazole derivative from sulfadoxine was smoothly converted, yielding 54% of **52** using HCl at room temperature. Interestingly, when MgCl$_2$ at high temperature was used instead, chlorination was accompanied by a demethylation of one –OMe group from the pyrimidine (Supplementary Information, page 36 for details). Finally, another anti-cancer medication such as dabrafenib was also similarly subjected to chlorination, obtaining 40% of **53**. To fully benchmark the usefulness of the protocol developed herein, some of the most critical examples were also tested under state-of-the-art Sandmeyer conditions. Whereas **24**, **30** and **32** could be obtained under Sandmeyer conditions, the yields were comparably lower than when our protocol was applied. Although the Sandmeyer conditions were not optimized for each substrate and a general protocol was applied, no product was detected in any of the other ten challenging substrates tested. Decomposition of the compounds leading to intractable mixtures was the general trend.

Unlocking a late-stage deaminative chlorination strategy permits the incorporation of all the well-known reactions for aryl halides to be applied in a late-stage functionalization context (Fig. 3a). For example, C(sp^2)–C(sp^2), C(sp^2)–C(sp^3) and C(sp^2)–C(sp) cross-couplings can now be carried out in substrates where such reactivity was limited (Negishi **54**, Suzuki **55** and Sonogashira **56**).

Table 1 | Substrate scope of the deaminative chlorination of aminoheterocycles
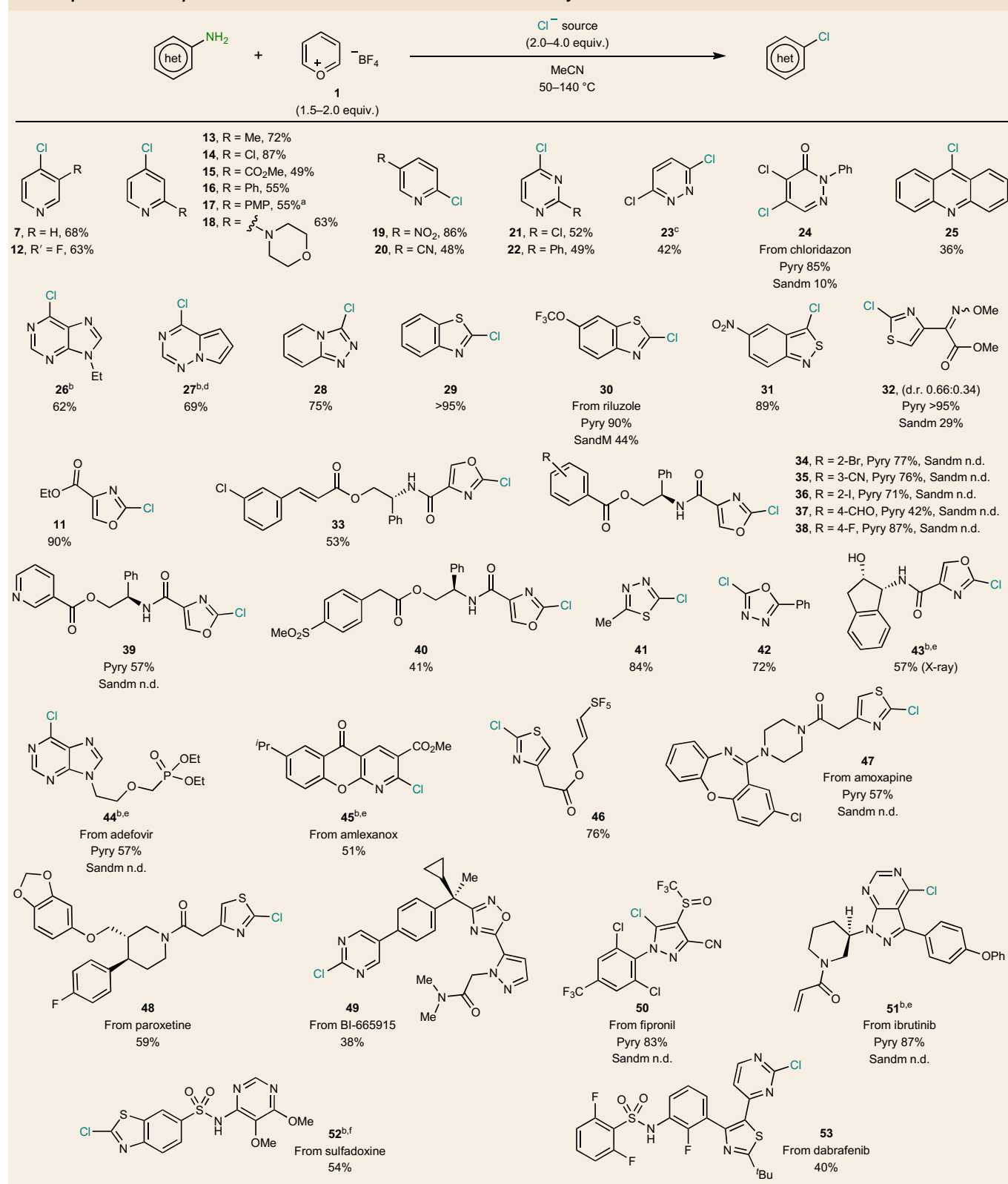
Unless otherwise stated, reactions were conducted in a one-step procedure as follows. Pyry, general conditions: aminoheterocycle (1 equiv.), 1 (1.5 equiv.), MgCl$_2$ (2.0–5.0 equiv.), CH$_3$CN (0.1 M), 50–140 °C, 16 h. Sandm, Sandmeyer conditions: aminoheterocycle (1 equiv.), NaONO (1.1 equiv.); HCl (aq) 37% (0.2 M), 0 °C, 15 min; then, CuCl (1.3 equiv.), 25 °C, 3 h. For compounds 34–38, 2 = *ortho*, 3 = *meta*, 4 = *para*. [a]PMP = 4-methoxyphenyl. [b]Two-step procedure: pyridinium formation then chlorination. [c]CsCl (4 equiv.) instead of MgCl$_2$. [d]Me$_4$NCl (4 equiv.) instead of MgCl$_2$. [e]^{n}Bu$_4$NCl (4 equiv.) instead of MgCl$_2$. [f]HCl (1 M) in Et$_2$O (4 equiv.) instead of MgCl$_2$. n.d., not detected; het, heterocycle.

Nucleophilic aromatic substitution, one of the most robust and utilized reactions with aryl halides, is also within reach; aliphatic amines, both primary and secondary, including duloxetine, can be incorporated in high yields through simple protocols (57, 58). Secondary alcohols such as cholesterol can be easily decorated with a benzothiazole group in good yield (59). Other nucleophiles, namely
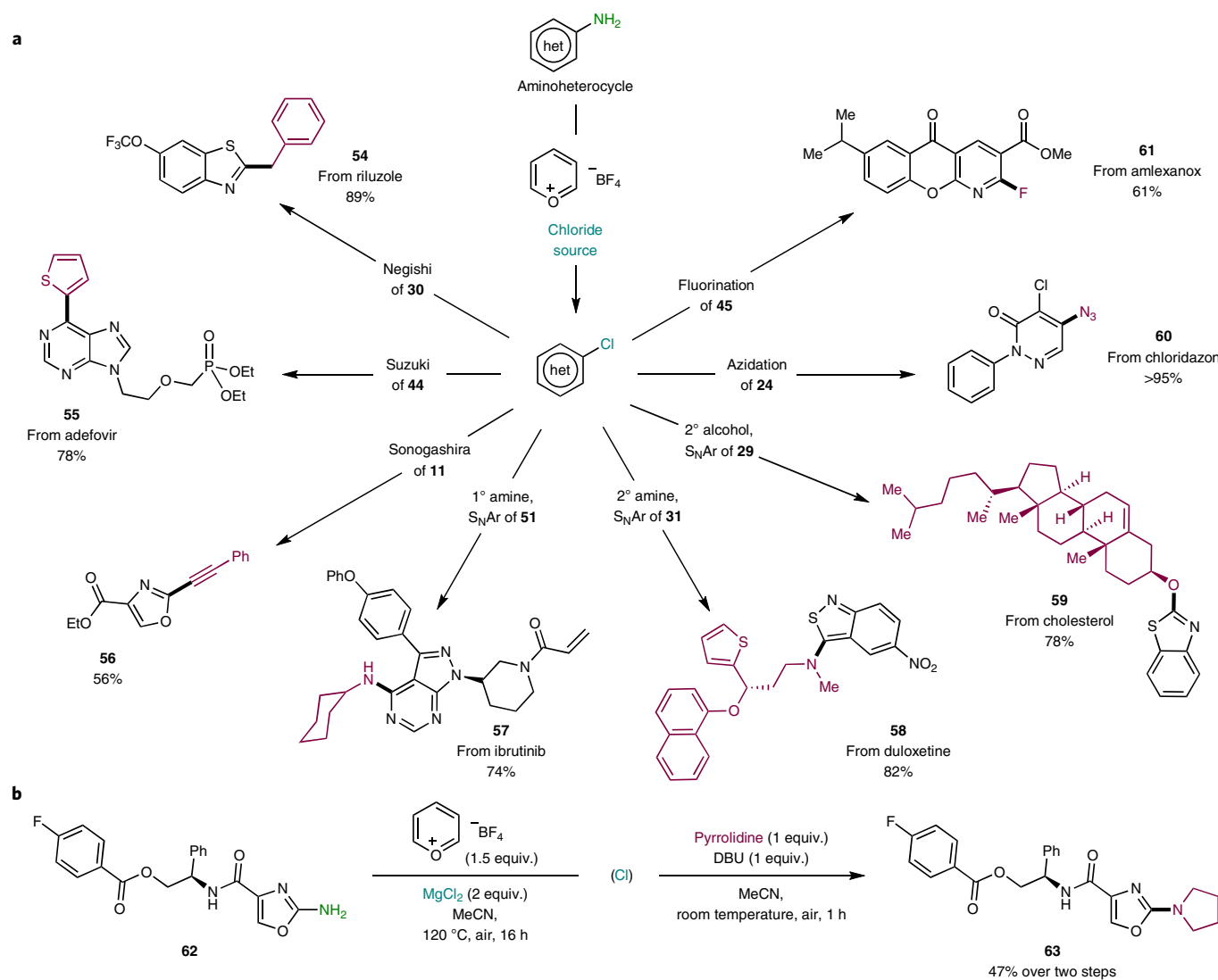
Fig. 3 | Deaminative chlorination bridges the wide availability of aminoheterocycles with the powerful chemistry of aryl chlorides. a, Examples of derivatization of aryl chlorides from the parent aminoheterocycle. Details for the procedures for each particular example can be found in the Supplementary Information, section VI, 'Post-functionalization'. **b**, Telescoped deaminochlorination followed by nucleophilic aromatic amination. DBU, 1,8,-diazabicyclo[5.4.0]undec-7-ene; 1°, primary; 2°, secondary; S$_N$Ar, nucleophilic aromatic substitution.

fluoride and azide, were also engaged and displaced the Cl atom, leading to valuable products (**60**, **61**). With the aim of highlighting the practicality of the method, a telescoped three-step sequence to the pyrrolidine-functionalized analogue of **62** was attempted; **63** could be obtained in 47% yield without the need for purification of the pyridinium or chlorinated intermediate (Fig. 3b).

The scalability of the protocol was demonstrated by the gram-scale reaction performed on **64** without erosion of the yield (**32**; Fig. 4a). The deaminative halogenation was also extended to other halogens. For example, both five- and six-membered rings could be smoothly brominated using simple LiBr or MgBr$_2$ (**66** and **68**; Fig. 4b). To test the limits of our protocol, fluorides were also considered as nucleophiles. In contrast to the chlorination or bromination, fluorination required preformation of the pyridinium salt, followed by the addition of rigorously dried KF (Fig. 4c). In this case, C(sp^2)–F bond formation occurs in moderate to good yields, as demonstrated by the five examples reported (**69**–**73**). When the exclusion of water is not possible, the pyridine ring-opened products are obtained (Supplementary Information, page 47 for details)[29,30]. In the case of milder nucleophiles such Cl or Br, the attack on the pyridinium might be reversible and occur in both C2

and C4 (ref. [31]). It is not until the *ipso* position is attacked that the process becomes irreversible and ultimately leads to the formation of pyridine and the aryl chloride (Fig. 4d).

Conclusions

Inspired by natural deaminases, we herein report a synthetic tool that enables the conversion of C(sp^2)–NH$_2$ groups into C(sp^2)–Cl in high chemoselectivity under mild conditions. The use of the simple Pyry-BF$_4$ selectively targets the NH$_2$ attached to a heterocyclic motif and primes it for reactivity by converting it into a pyridinium intermediate, which further reacts with a chloride source. This protocol merges the potential of the venerable Vilsmeier reaction to decorate aromatic heterocycles, with the ubiquity of aminoheterocycles, resulting in a deaminative chlorination protocol that avoids the use of explosive intermediates or strongly oxidizing reagents. As a result, the high chemoselectivity permits the chlorination of >40 compounds containing a myriad of functional groups, embedded in >20 different aminoheterocycles including five- and six-membered rings. The method is easily scalable, without the need for air-extrusion and without problematic runaway exotherms. Deaminative bromination of the amino group has also
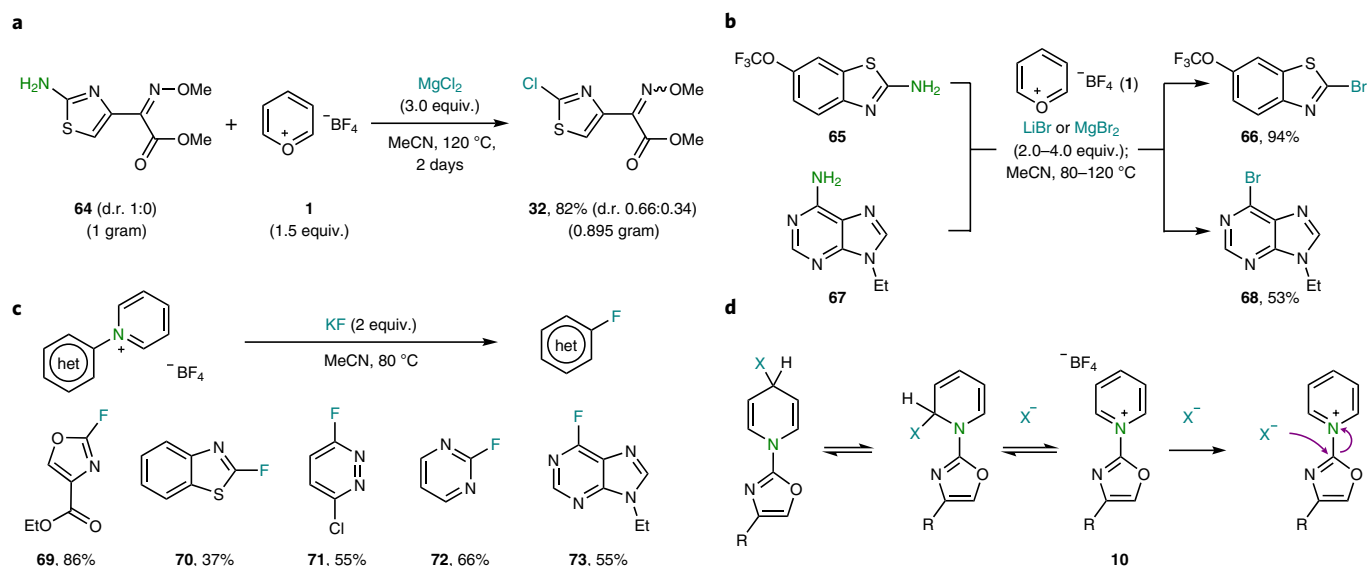
Fig. 4 | Beyond deaminative chlorination. a, Scalability of the process. **b**, Deaminative bromination. Reaction conditions: aminoheterocycle (1 equiv.), **1** (1.5 equiv.), EtOH (1 ml), 80 °C, 16 h; then the solvent is removed followed by the addition of the Br source (4 equiv.), CD₃CN (1 ml), 80–120 °C, 16 h. **c**, Fluorination of pyridinium salts. Reaction conditions: pyridinium salt (1 equiv.), KF (2 equiv.), CH₃CN (1 ml), 80 °C, 1–16 h. **d**, Tentative mechanism of the deaminative halogenation.

been demonstrated with a similar efficiency. More importantly, this deaminative chlorination protocol was applicable to the late-stage chlorination of various drugs and agrochemicals, thus permitting post-modification of complex structures beyond the realms of the Sandmeyer reaction. The method has been shown to extend to other halogenation processes, namely bromination and fluorination. We believe this methodology provides practitioners with an alternative tool that will permit the scrutiny of unexplored chemical space and ultimately accelerate the drug discovery process.

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Methods

General procedure for the chlorination of amino heteroaromatic compounds.
Unless otherwise specified, an 18 ml screw-capped tube under normal atmosphere is charged with pyrylium tetrafluoroborate **1** (1.5 equiv.) and MgCl$_2$ (2.0 equiv.). The starting material (1.0 equiv.) is then added and directly followed by CH$_3$CN (0.1 M). The resulting mixture is then stirred 5 minutes at 25 °C and then 16 hours at 120 °C. The reaction is allowed to cool to 25 °C. The crude mixture is partitioned between water and EtOAc. The aqueous layer is extracted with EtOAc (3 × 10 ml). The combined organic layers are dried over Na$_2$SO$_4$, concentrated to dryness and purified on silica gel to afford the desired product.

Data availability

The Supplementary Information contains all experimental procedures and analytical data (^{1}H, ^{19}F, ^{31}P, ^{13}C, high-resolution mass spectrometry and crystallographic data) for all compounds, all reversibility experiments and the complete optimization study as well as a limitations section. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2070324 (**43**) and 2086010 (**52′**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

Acknowledgements

Author contributions

C.G. optimized the process, designed the approach, performed the experiments, analysed the experimental data, prepared the Supplementary Information and helped in the manuscript preparation. T.F. contributed to expanding the applicability of the protocol to certain five-membered rings. A.G.-P. contributed at the initial stages of the project and found conditions in the chlorination and bromination. J.C. conceived the idea, directed the investigations and prepared the manuscript.

Funding

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41557-021-00812-0.

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Peer review information *Nature Chemistry* thanks Patrick Fier and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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