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Late-Stage Functionalisation of Pyridine-Containing Bioactive Molecules: Recent Strategies and Perspectives

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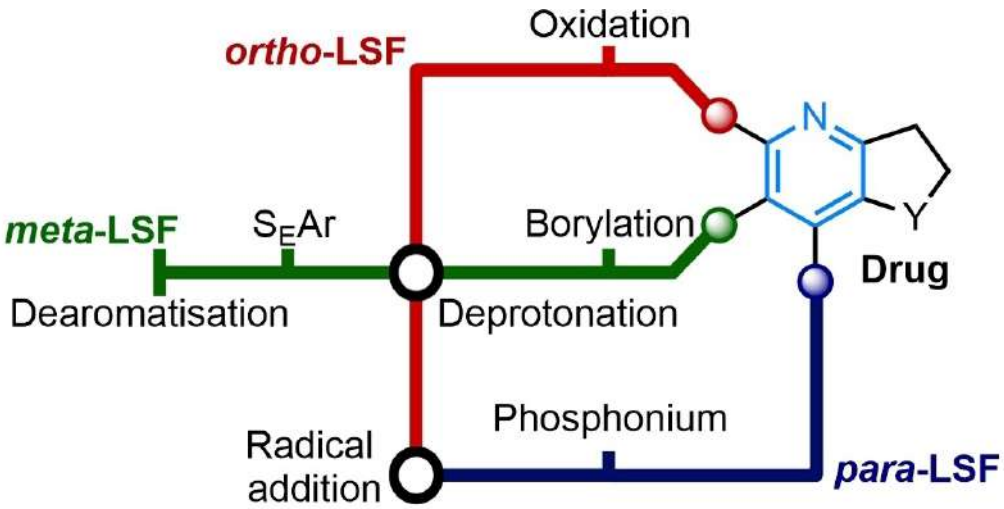

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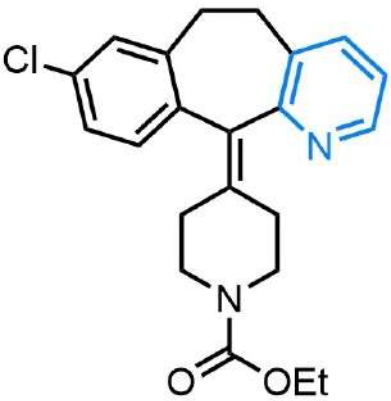

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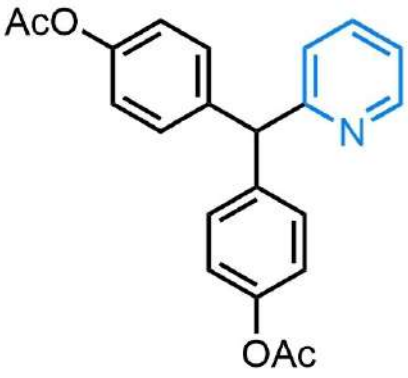

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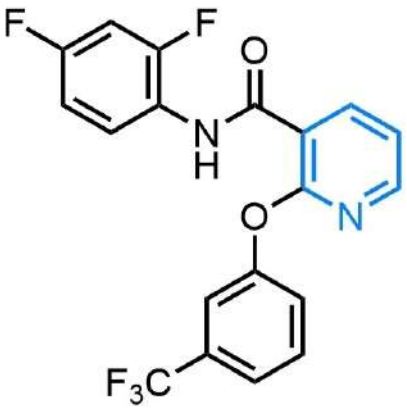

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Late-Stage Functionalisation (LSF) is an innovative technique that has been successfully applied to the C–H diversification of pharmaceuticals. However, LSF of the pyridine ring in drug-like molecules is often unselective. As a result, a mixture of structurally related products is obtained, thus making the purification tedious and time-consuming. This review shines a light on recent strategies addressing the selectivity issue in the LSF of complex natural products or drugs containing the pyridine moiety. Specifically, we have reviewed the efforts reported both in academia and industries with the hope of providing a guide for the LSF of elaborated pyridines.

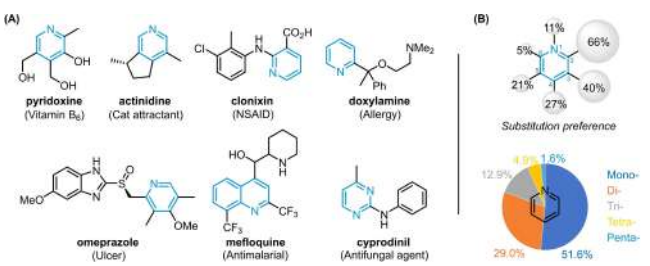
1. Introduction

In the past decade, the direct functionalisation of inactivated C–H bonds has emerged as a powerful technique to access novel chemical entities.[1] Indeed, C–H functionalisation methods offer the opportunity to explore chemical space more effectively than relying solely on conventional synthetic approaches.[2] Late-stage functionalization (LSF) is a synthetic approach that involves performing C–H transformations on complex molecules, showcasing high chemo- and site-selectivity and usually not requiring preinstalled functional groups, thus allowing for the creation of new analogues without de novo synthesis.[3–10] From the perspective of pharmaceutical industries, LSF approaches offer efficient entries into unexplored structure–activity relationship (SAR); improvement of key pharmacokinetics properties; incorporation of synthetically useful handles for further bioconjugation/chemical biology efforts, and access to new intellectual property space using reaction vectors left unexplored by conventional synthetic methods. Despite LSF having been successfully applied to the C–H diversification of pharmaceuticals, pyridine-containing drug-like molecules are often problematic due to limited selectivity. In this review, we wish to provide medicinal chemists with a practical guide to address the selectivity issue in the late-stage functionalisation of pyridine-containing drugs. Indeed, while excellent reviews on C–H LSF methods focus mainly on the reaction manifolds enabling LSF,[11] we have reviewed LSF strategies for the selective decoration of pyridine-containing drug-like molecules being this heterocycle the most used *N*-aromatic among all U.S. FDA approved pharmaceuticals.[12]

1.1. LSF of pyridine-containing bioactive molecules

More than 90% of marketed small molecule drugs incorporate a heterocyclic structure, a cyclic carbon motif containing at least another element as a member of its ring.[13] Among heterocycles, nitrogen-containing aromatic heterocycles are of significant relevance, with pyridines and quinolines among the most prevalent structural units in natural products and synthetic drugs (Scheme 1A).[12] Moreover, substitution-type analysis of pyridine-containing drugs revealed a different degree of substitution of the ring, ranging from the predominant mono-substitution up to penta-substitution (Scheme 1B). However, despite the prevalence of this aromatic ring in many bioactive molecules, the selective functionalisation of this heterocycle is often problematic. Specifically, both electrophilic *ortho*- and *para*-positions are sometimes hard to discriminate, thus yielding a mixture of products whose purification is tedious and time-consuming. Moreover, *meta*-functionalisation is rather unexplored, limiting the chemical space exploration on this site.[14]

In this review, we aim to shine a light on recent strategies addressing the selectivity issue in the late-stage functionalisation of pyridine-containing drugs, critically assessing how selectivity has been achieved in *ortho*-, *meta*-, and *para*-positions of the pyridine ring. This review does not include LSF examples where complex pyridines undergo ring rearrangements (e.g. contraction or expansion) since covered elsewhere in the literature.[15]



Scheme 1. (A) Examples of pyridine-containing bioactive molecules; (B) Pyridine substitution patterns in drugs.

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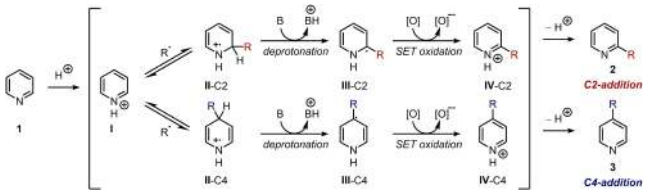
2. *ortho*-Selective LSF

The *ortho*-position of pyridines is the preferred substituted site. LSF at this position exploits the innate electrophilic character of its carbon, thus addition-elimination reactions (typically with nucleophilic radicals) represent the main strategy of functionalisation. Moreover, being in alpha to the nitrogen atom, *ortho*-functionalisation can also be achieved by means of deprotonation or oxidation.

2.1. *ortho*-Addition of radicals

The functionalisation of *N*-heteroarenes with radicals is widely known as the Minisci reaction (Scheme 2).[16–18] A variety of carbon-centered radicals (e.g. alkyl, aryl, trifluoromethyl, acyl radicals) have been successfully employed in the Minisci reaction, thus allowing for wide functionalisation of pyridine rings. Acid is commonly used as a stoichiometric additive as protonation of the pyridine **1** facilitates the addition of the nucleophilic radical, thus yielding the radical cation **II**. This intermediate can then formally lose a hydrogen atom via a hydrogen atom transfer (HAT) process or via deprotonation, followed by a single electron transfer (SET) event, yielding the functionalised pyridinium **IV**.

However, since the electrophilicity at C2- and C4-position is often very similar, a mixture of regioisomers **2** and **3** is usually obtained. Nevertheless, the regioselectivity is affected by several factors (e.g. the nature of the radical, the solvent polarity, the Brønsted acid used), thus Minisci-type reactions have been employed in selective late-stage functionalisations, especially for the *ortho*-position. In this scenario, the typical reaction conditions (e.g. elevated temperatures, strong acid or oxidants) may not be compatible with complex *N*-aromatic structures, therefore many milder alternatives have been developed, especially addressing the radical generation. From this point of view, photocatalysis has become an efficient method for the generation of radicals, as reported by MacMillan and co-workers in their pioneering studies.[19] Building on this seminal work, the merger of photoredox catalysis (SET processes enabled by a catalyst excited by visible light) and thiol-based HAT catalysis have been successfully applied for the late-stage functionalisation of elaborated pyridines, with the vasodilator milrinone **4** being an interesting example (Scheme 3).[20] However, in this case, the *ortho*-selectivity has been achieved by blocking the C4-position, as demonstrated by the fact that the simple quinoline gave a mixture of regioisomeric products under identical reaction conditions.

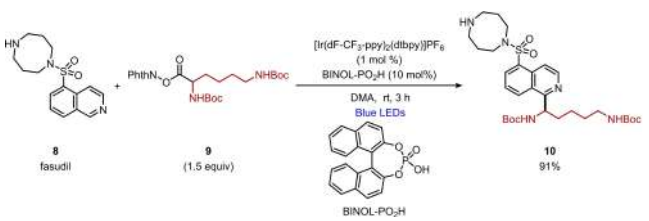


Scheme 2. Minisci reaction mechanism (**II** to **IV** via HAT not shown).

Scheme 3. Photocatalytic alkylation of milrinone.

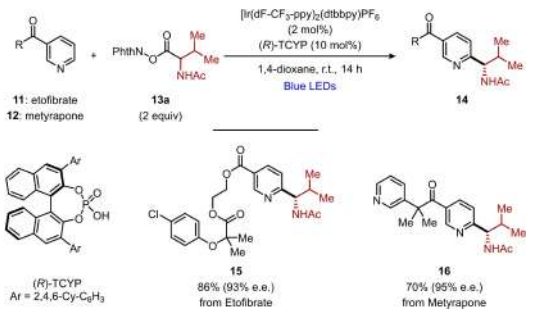
The method reported by MacMillan and co-workers is innovative since the use of alcohols as latent alkylating agents has been elusive. Indeed, redox-active esters are usually employed as carbon-radical precursors, with applications in late-stage functionalisation successfully demonstrated in the case of fasudil **8**, a Rho-kinase inhibitor and vasodilator (Scheme 4).[21]

In this case, *N*-Hydroxyphthalimide **9** (NHPI) is the redox-active ester which, upon SET from the excited iridium catalyst under blue-light irradiation, fragments losing carbon dioxide, phthalimidyl anion and the corresponding C(sp^3)-radical. It is important to note that NHPIs are easily derived from the corresponding carboxylic acids, thus starting with amino acids (e.g. lysine in this case) allows for α-aminoalkylation of the pyridine ring. Moreover, the use of BINOL-based phosphoric acid as protonating agent is very appealing since it can be exploited in asymmetric synthesis, as later was demonstrated by Phipps and co-workers for etofibrate **11** and metyrapone **12** (Scheme 5).[22] The latter, an inhibitor of cortisol biosynthesis, is a beautiful example of a chemo-, regio-, and enantioselective functionalisation of a complex pyridine-containing drug. Notably, the stereocontrolled addition of the prochiral radicals is achieved via two hydrogen-bonding interactions of the enantiopure chiral Brønsted acid catalyst with the substrate and the α-



Scheme 4. Photocatalytic aminoalkylation of fasudil.

Valerio Fasano received his PhD at the University of Manchester, under the supervision of Prof. Michael Ingleson. He then joined the group of Prof. Varinder Aggarwal (University of Bristol) as a Research Fellow. In 2022, he moved to the University of Milan as an Assistant Professor (with Prof. Daniele Passarella). His research interests include selective functionalisations of pyridines and the synthesis of bioactive N-heterocycles.



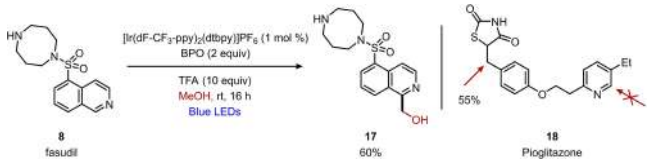
Scheme 5. Enantioselective aminoalkylation of etofibrate and metyrapone.

aminoalkyl radical, probably also explaining the high *ortho*-regioselectivity.

Photocatalysis has also been employed for the mild generation of α-hydroalkyl radicals, as opposed to the initial Minisci reports which used ammonium persulfate and sulfuric acids. This has been successfully employed by DiRocco, Krska, and co-workers in their photoredox-catalysed hydromethylation of fasudil **8** (Scheme 6).[23] In this case, benzoyl peroxide (BPO) was used as the oxidant to close the iridium catalytic cycle. However, this methodology could not be extended to other elaborated drugs, as demonstrated by the lack of pyridine functionalisation for pioglitazone **18** where the benzylic position was instead activated. Moreover, the *ortho*-selectivity was achieved by blocking the C4-position (i.e. 2-phenylpyridine gave a mixture of *ortho*- and *para*-hydroxymethylated products).

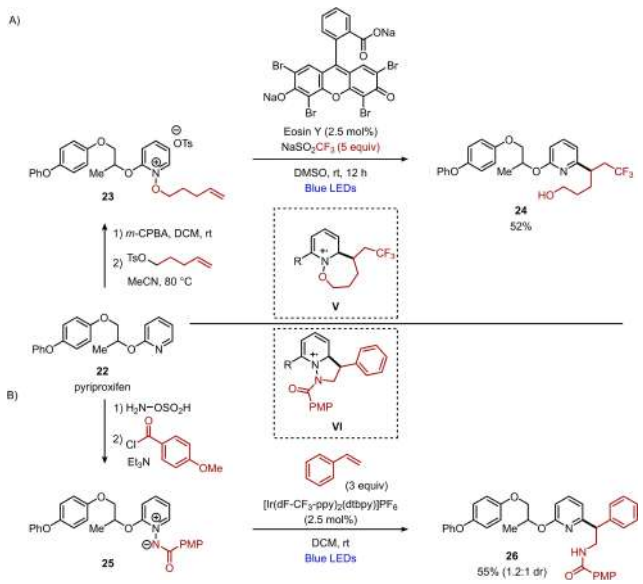
The examples so far have shown how the iridium catalysts was essential to trigger single-electron processes under blue-light irradiation. Nevertheless, in the last decade many efforts have been devoted to the replacement of the precious and expensive iridium catalysts with cheaper photocatalysts. An interesting contribution is the use of $Mn_2(CO)_{10}$ as an earth-abundant metal photocatalyst, in combination with alkyl iodides as the radical precursors, as reported in the late-stage functionalisation of bosutinib **19** (Scheme 7).[24] This tyrosine kinase inhibitor is an intriguing example of functional group tolerance, yet the *ortho*-selectivity is obtained by blocking the C4-position, as in the other many examples reported in this work.

Photocatalysis can be also performed under transition metal-free conditions using organic photoredox catalysts.[25] Among them, Eosin Y, a brominated fluorescein, has gained significant attention being a cheap, widely available photocatalyst.[26] For instance, Hong and co-workers have exploited the photoredox properties of Eosin Y for the selective *ortho*-functionalisation of the pesticide pyriproxyfen **22** (Scheme 8A).[27] In this process, the pyridine was first converted into the corresponding *N*-alkoxypyridinium salt by sequential oxidation with *m*-chloroperbenzoic acid, followed by an S_N2 reaction between the pyridine *N*-oxide and an alkyl tosylate. *N*-alkoxy pyridinium salt **23** was then subjected to the photoredox process where, upon addition of a $-CF_3$ radical to the terminal alkene, the resulting nucleophilic alkyl radical added to the pyridinium salt to give radical cation intermediate **V**. Subsequent cleavage of the N–O bond delivered the fluoroalkylated pyridine derivative. Interestingly, this strategy was not limited to secondary alkyl radical intermediates but could also be extended to tertiary radicals, thus furnishing products containing quaternary carbons. It has to be noted that the designed *N*-alkoxypyridinium salt **23** ensured that the tethered radical engaged in an intramolecular *endo*-addition only onto the *ortho*-position. Indeed, if not tethered, modest regioselectivity (*ortho* vs. *para*) was observed in the trapping of *N*-alkoxypyridinium salts with secondary alkyl radicals, whereas tertiary alkyl radicals provided exclusively *para*-functionalisations. The same group reported a conceptually similar *ortho*-functionalisation on pyriproxifen **22**, combining *N*-aminopyridinium ylides with alkenes, in the presence of acridinium- or iridium-based photocatalysts (Scheme 8B).[28] *N*-aminopyridinium ylide **25** acts as a bifunctional reagent to enable *ortho*-selective aminopyridyla-



Scheme 6. Photocatalytic hydroxymethylation of fasudil.

Scheme 7. Photocatalytic alkylation of bosutinib.



Scheme 8. Photocatalytic alkylation of pyriproxifen.

tion of styrene by a radical-mediated 1,3-dipolar cycloaddition via radical cation **VI**.

Another important class of organic photoredox catalysts are based on *N*-methyl-acridinium salts, with the 9-mesityl derivative being among the most employed one.[29] This photoredox catalyst has been widely applied in a range of useful transformations, including late-stage alkylation of the antimalarial drug quinine **27** (Scheme 9).[30] In this case, alkyl trifluoroborate **28** outperformed alkyl iodide as radical precursors, although the former needed to be synthetised most of the time. Notably, the authors noted an enhanced *ortho*-selectivity compared to standard Minisci-type reactions. This was attributed to the coordination of by-product BF_3 to the heterocycle prior to the radical addition, thus enhancing the C2-preference beyond the activation provided by the added protic acid.

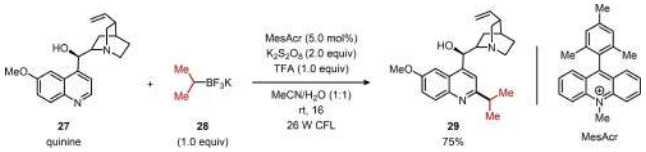
As seen before, Minisci-type reactions often involve the addition of carbon-centered radicals to protonated *N*-heteroarenes. Depending on the structure of the radical, different functionalities could be tethered to the added carbon moiety. A different strategy exploits instead boron-centered radicals, as recently reported by Leonori and co-workers in their late-stage borylation of the fungicide quinoxyfen **30** (Scheme 10).[31] Using amine-borane reagent **31** as radical precursors and 4CzIPN as the organic photocatalyst, Minisci-type reactivity enabled the installation of the $-BH_2NMe_3$ group which could then be transformed into a variety of other functional groups. It has to be noted that while the *ortho*-selectivity was achieved by blocking the C4-position (i.e. quinoline gave a mixture of regioisomers), this strategy is complementary to C3-H transition metal-catalysed borylation (see below).

Finally, using carboxylic acid **34** as the radical precursor, the merging of photocatalysis with electrochemistry has also enabled selective *ortho*-functionalisation, as reported for chlorantraniliprole **33**, an insecticide of the ryanoid classes (Scheme 11).[32] Electrophotochemical methods also enabled deaminative alkylation of pyridine-containing drugs using Katritzky salts as radical precursors (see section 6 for Loratadine).[33]

While photocatalysis has prompted the renaissance of radical chemistry, alternative strategies for the generation of radicals have been introduced too. In this area, the work of Baran has shown how zinc sulfinate reagents are powerful radical precursors when treated with an oxidant.[34] Many of these reagents are now commercially available and have been employed in the late-stage functionalisation of N-heterocycles, as shown for nevirapine **36**, a non-nucleoside reverse transcriptase inhibitor (Scheme 12).[35] This example highlighted the chemoselectivity of the reaction, with the nucleophilic *i*-Pr radical from zinc sulfinate **37 a** engaging preferentially with the more electron-deficient pyridine ring instead of the electron-rich pyridine.

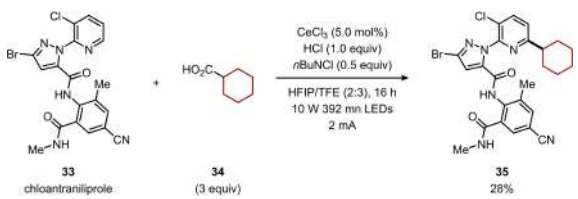
$C(sp^3)$-centered alkyl radicals can also be prepared from the homolysis of 1,4-dihydropyridines **43** (DHPs), species readily prepared from aldehydes **42** in one step (Scheme 13A).[36]

While delivering the same radical, DHPs are preferred over aldehyde precursors since no acylated by-products can be formed during the oxidative radical generation. Minisci-type chemistry using DHPs has been applied to the late-stage alkylation of many elaborated pyridines, including fasudil **8**, quinine **27** and nicotine **44** (Scheme 13B).[37] The *ortho*-

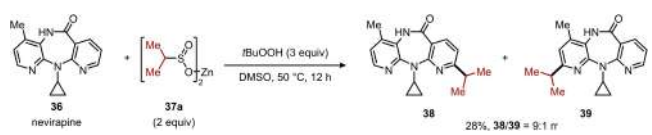


Scheme 9. Photocatalytic alkylation of quinine.

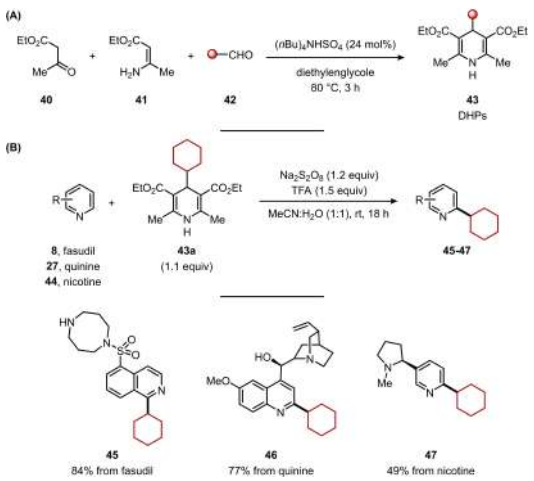
Scheme 10. Photocatalytic borylation of quinoxyfen.



Scheme 11. Electrophotocatalytic alkylation of chlorantraniliprole.



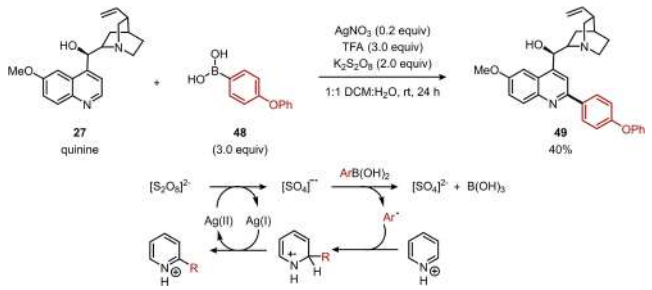
Scheme 12. Alkylation of nevirapine with zinc sulfinates.



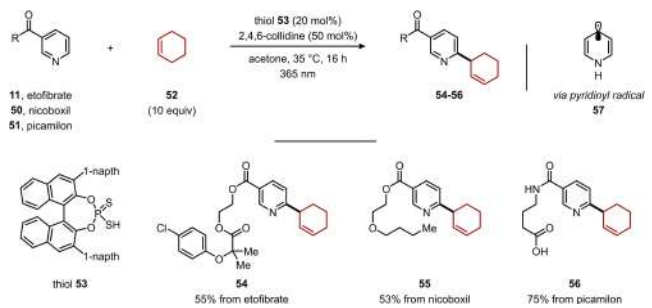
Scheme 13. (A) Preparation of DHPs; (B) Alkylation of fasudil, quinine and nicotine with DHPs.

selectivity in this case probably arises from the steric hindrance provided by the pyrrolidine moiety since in other cases (e.g. quinoline) double alkylation at C2- and C4-position was observed. Minisci's conditions for the oxidative decarboxylation of alkylcarboxylates fails on their aryl counterparts, thus preventing the formation of C(sp^2)-centered aryl radicals. However, it has been shown that the use of arylboronic acids could overcome this limitation, as reported for the late-stage arylation of quinine **27** (Scheme 14).[38] This natural product contains an oxidizable benzyl alcohol, an electron-rich mono-substituted alkene, and a highly nucleophilic quinuclidine-type nitrogen, yet arylated product **49** could be obtained in 40% yield. In this case, the homolytic cleavage of the C–B bond in arylboronic acids could be induced in a manner similar to the decarboxylation of alkylcarboxylates by using catalytic silver nitrate in the presence of persulfate. The widespread availability of boronic acids, along with the possibility to direct install an aryl group (as opposed to Scheme 10), make this strategy very appealing for late-stage functionalisations.

Finally, an innovative *ortho*-functionalisation strategy based on radical additions has been recently applied by Melchiorre and co-workers in the late-stage allylation of etofibrate **11**, nicoboxil **50** and picamilon **51** (Scheme 15).[39] In contrast to Minisci-type reactions, this chemistry harnesses the reactivity of pyridinyl radicals **57**, generated upon single-electron reduction of pyridinium ions. These radicals are then coupled with allylic radicals generated via thiol-based HAT catalysis with thiol **53**. It has to be noted that the *ortho*-selectivity was observed for pyridines bearing bulky 3-substituents, whereas simpler substrates gave C4-functionalisation. While the *para*-regioselectivity could be explained by the greater spin density at C4, the stereoelectronic factors dictating the *ortho*-regioselectivity were still unclear.



Scheme 14. Arylation of quinine with boronic acids.



Scheme 15. Allylation of pyridines via pyridinyl radicals.

2.2. *ortho*-Deprotonation strategies

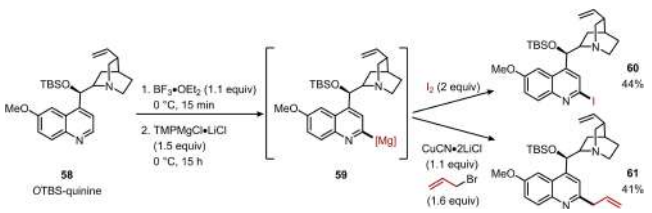
As seen in Schemes 13 and 14, Minisci-type conditions allow the selected C2-arylated of quinine **27**. This natural alkaloid – protected as silyl ether **58** - has been functionalised in the same position using a deprotonation strategy, as reported by Knochel and co-workers (Scheme 16).[40] In particular, upon activation of the pyridine ring via coordination with BF_3, the hindered base 2,2,6,6-tetramethylpiperidyl-magnesiumchloride (TMPMgCl·LiCl) selectively deprotonated the *ortho*-position. The obtained metalated species **59** is then reacted with an electrophile, obtaining the corresponding products **60** and **61** in moderate yield. Notably, the quinuclidine nitrogen usually directs the metalation in *meta*-position (see section 3.2), but the steric hindrance provided by the nearby *tert*-butyldimethylsilyl (TBDMS) group prevented this competitive deprotonation pathway.

2.3. *ortho*-Oxidation strategies

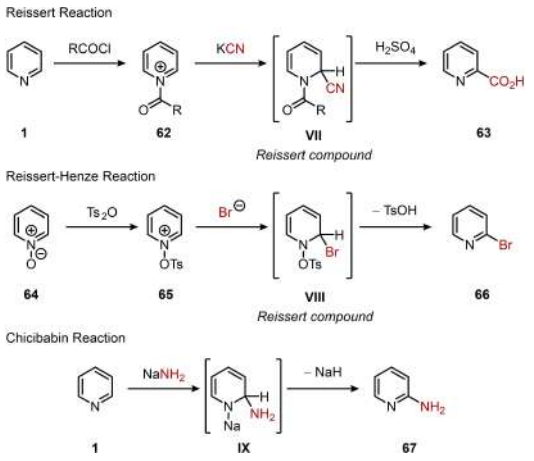
In Minisci reactions, upon the addition of a nucleophilic radical to a protonated *N*-heteroarene, a hydrogen atom is lost via HAT or deprotonation/SET sequence. An analogous strategy can be performed in a two-electron process (i.e. polar reaction), with the Reissert reaction of pyridine **1** and the Reissert-Henze reaction of pyridine *N*-oxide **64** being two typical cases (Scheme 17).[41]

These reactions represent an important mode of selective *ortho*-functionalisation, as demonstrated by the late-stage bromination of quinine **27** reported by Baran and co-workers using Ts_2O to activate the *N*-oxide and TBABr as brominating agent (Scheme 18).[42] Notably, a low concentration of the *N*-oxide was critical to prevent C2-addition of the tosylate anion, as well as to prevent undesired bromination at the C8 position. The authors also developed a one-pot oxidation/bromination employing methyltrioxorhenium/urea hydroperoxide (UHP) as the oxidant, thus removing the need to isolate the pyridine *N*-oxide (shown for 6-methoxyquinoline **70**).

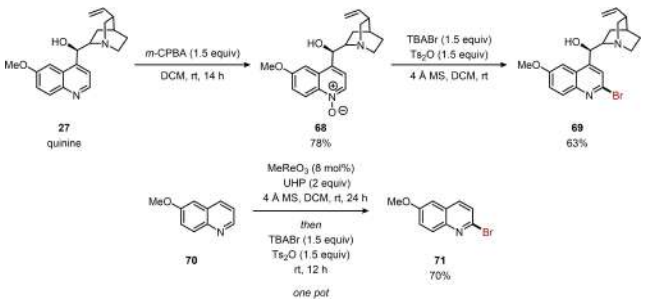
A Reissert-Henze type reaction that does not require pyridine *N*-oxide formation has been recently developed by Fier and co-workers, as demonstrated in the late-stage amination of



Scheme 16. Metalation of quinine and subsequent electrophilic trapping.

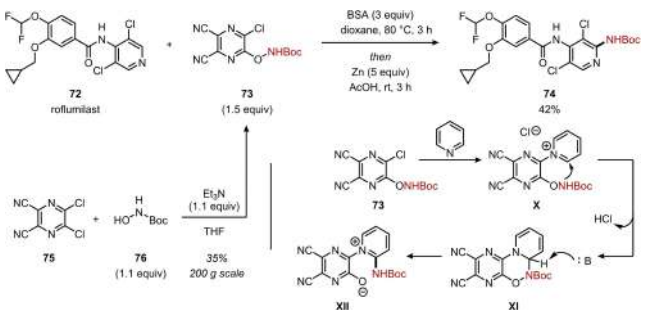


Scheme 17. Reissert, Reissert-Henze and Chichibabin reactions.



Scheme 18. Bromination of quinine.

roflumilast **72**, a phosphodiesterase inhibitor with anti-inflammatory properties (Scheme 19).[43] In particular, the authors designed the electro-deficient chloropyrazine **73** as the activator as well as the aminating reagent. Notably, this crystalline, air-stable reagent could be prepared in large quantities starting from cheap, commercially available 5,6-dichloropyrazine-2,3-dicarbonitrile **75** and *tert*-butyl hydroxycarbamate **76**. Upon pyridine activation via an S_NAr reaction on **73**, an intramolecular delivery of the nitrogen nucleophile, followed by rearomatization through N – O bond cleavage and tautomerization, yields intermediate **XII**. In this step, the scavenging of HCl with inorganic or organic bases led to the decomposition of the chloropyrazine, whereas the use of *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) was successful through the generation of TMSCl. Treatment of **XII** with metallic zinc allowed then the reductive cleavage of the pyrazine fragment.

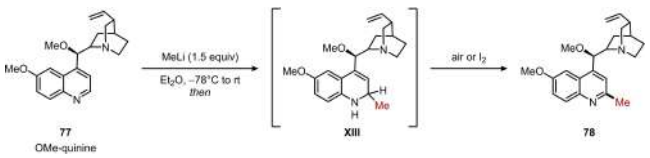


Scheme 19. Roflumilast amination.

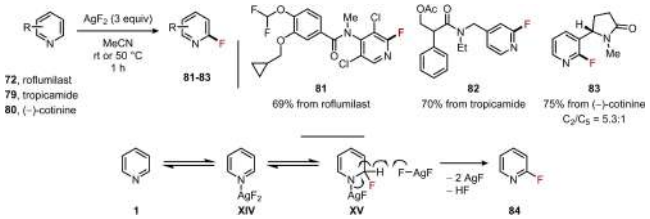
It has to be noted that the protocol developed by Merck, in contrast to the Chichibabin reaction, allows amination under mild conditions, thus compatible with late-stage functionalisations. Indeed, in the Chichibabin reaction, *ortho*-amination is usually achieved by direct addition of a strong nucleophiles such as $NaNH_2$ in liquid ammonia, followed by hydride elimination (Scheme 17).[44] A similar strategy has been shown using MeLi as nucleophiles, with the corresponding 1,2-dihydropyridine **XIII** then oxidised in air or with iodine (Scheme 20).[45]

This method allowed the selective *ortho*-methylation of 9-*O*-methylquinidine **77**, but despite appealing, the use of a strong nucleophile/base such as MeLi may be incompatible with susceptible functionalities present in other elaborated pyridines. Halides are less nucleophilic than $NaNH_2$ or MeLi to give direct addition to pyridine, thus *ortho*-halogenation is usually achieved by Reissert-Henze type reactions, as discussed above. However, halogenation without using pyridine *N*-oxides has been reported by Fier and Hartwig in their selective *ortho*-fluorination of several bioactive molecules, such as roflumilast **72**, tropicamide **79** and (−)-cotinine **80** (Scheme 21).[46] The installed fluoride was then used for further functionalisations via nucleophilic aromatic substitution (S_NAr) reactions.[47]

The authors identified AgF_2 as the ideal fluorinating agent since, other than being a source of nucleophilic fluoride, it binds to the pyridine (intermediate **XIV**) increasing the electrophilicity in *ortho*-position. Moreover, AgF_2 can act as an oxidant to aromatise the dihydropyridine intermediate **XV**. Notably, no quenching of the stoichiometric by-product HF was required in the process, as demonstrated by the fact that the addition of a base did not affect the yield or scope. It is worth mentioning that the light-insensitive AgF_2 is commercially available in kilogram quantities and is cheaper than many common



Scheme 20. Quinine methylation.



Scheme 21. Fluorination of pyridines.

fluorinating reagents. Another interesting oxidation strategy has been reported by Martin and co-workers in their late-stage silylation of pyridine-containing drugs (Scheme 22).[48] In this reaction, coordination of $[N(TMS)_2]^-$ to the boron atom of $Et_3SiBPin$ (Pin = pinacolato) triggers a nucleophilic addition of the corresponding silyl anion to the pyridine, the latter activated by coordination to K^+. It has to be noted that, while the intermediacy of the silyl anion has been proved by control experiments (and corroborated by the attack of the anion at the most electron-poor pyridyl backbone of **12** and **36**), the oxidation of the dearomatized *N*-BPin silylated azines is not fully understood. Notably, in the late-stage silylation of pharmaceuticals reported by the authors, electron-withdrawing groups direct the silylation at C2/C5, as for metyrapone and nevirapine (**12** and **36**), while for alkyl-substituted pyridines, such as nicotine and doxylamine, silylation takes place a C4 (**88** and **89**).

3. *meta*-Selective LSF

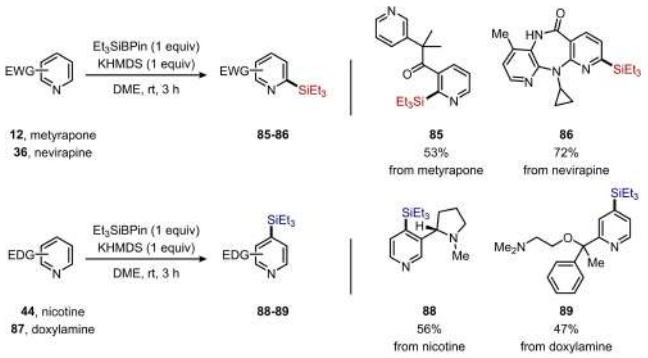
The *meta*-position of pyridine is hard to functionalise since this C–H bond does not have an innate reactivity. Therefore, *meta*-functionalisation is usually guided by a directing group or by sterics. This represents a limitation in LSF since usually requires the presence of a directing group in the starting pharmaceutical. Not surprisingly, *meta*-LSF are less common compared to the other two pyridine sites.

3.1. *meta*-Borylation strategies

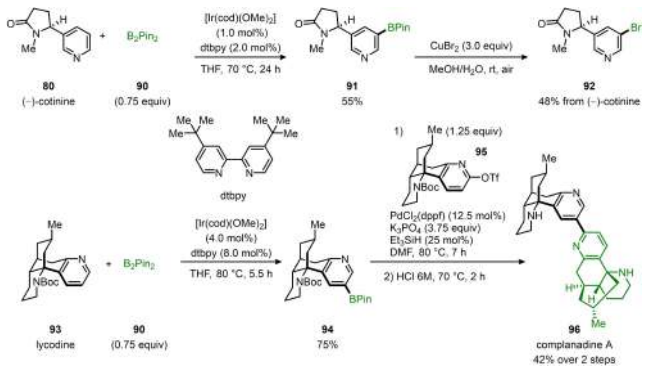
In the past decade, the iridium-catalyzed C(sp^2)–H borylation has become a widely used method for the functionalisation of arenes because of its ability to produce highly versatile aryl organoboronate ester intermediates from arenes without the need for reactive groups, such as halides or sulfonates.[49] However, when it comes to *N*-heteroarenes, the coordination of the nitrogen atom to the iridium often prevents catalytic turnover, as reported by Hartwig and co-workers in their detailed study on the borylation of *N*-heteroarenes.[50] Moreover, the authors have also shown that the C–H borylation of pyridines and quinolines occurs preferentially at the *meta*-position. Indeed, while C2-H borylation is usually slow and yields an unstable product, the C4-position is considered less sterically accessible, thus favouring a regioselective *meta*-borylation. This remarkable regioselectivity has been applied to the late-stage functionalisation of pyridine-containing alkaloids (Scheme 23).

Gallagher described the *meta*-selective borylation of (−)-cotinine **80** to access a broad range of unnatural derivatives upon conversion of unstable boronic ester **91** into 5-bromocotinine **92**.[51] Sarpong and co-workers described the *meta*-selective borylation of lycodine **93** in their total synthesis of (+)-complanadine A (**96**), an asymmetrical dimeric alkaloid of lycodine.[52] In particular, the authors applied the iridium-catalysed borylation to *N*-Boc-protected lycodine **93**, obtaining the desired C3-borylated product **94** in 75% yield. Suzuki cross-coupling of **94** with a triflate derivative of lycodine (**95**), followed by cleavage of the Boc-protective groups gave complanadine A in 42% yield over the two steps. Another successful late-stage *meta*-borylation of pyridines was reported by Hartwig and co-workers (Scheme 24).[53] Using antihistamine loratadine **97** as model drug, they used the iridium-catalysed borylation to selectively install the Bpin moiety in *meta*-position. The borylated intermediate was then converted in one-pot into the corresponding C3-methylated loratadine **99** using $PO(OMe)_3$ as the methylating agent. The use of $PO(OMe)_3$ to slowly release iodomethane was critical to ensure functional group tolerance to basic moieties such as unprotected amines, alcohols, or amides.

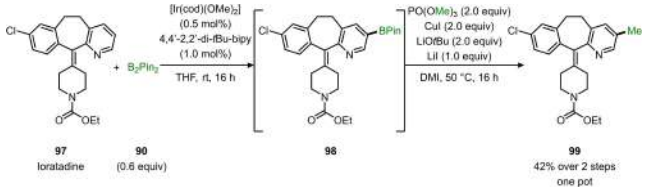
Meta-borylation is a powerful strategy for the late-stage functionalisation of N-heterocycles, also given the high versatility of the Bpin moiety. However, the iridium catalyst is expensive thus alternative functionalisations not based on



Scheme 22. Silylation of pyridine-containing drugs.



Scheme 23. C–H borylation of alkaloids.



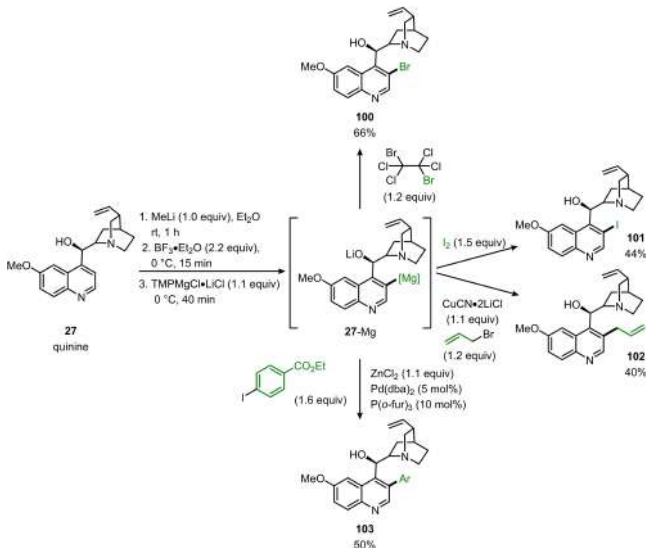
Scheme 24. C–H borylation of loratadine.

transition-metal catalysed C–H activation are still desirable, as reported in the following sections.

3.2. *meta*-Deprotonation strategies

As reported in section 3.3, Knochel and co-workers have developed a solid research program based on the selective C2-deprotonation of pyridines using the combination of the hindered base TMPMgCl·LiCl with BF_3·OEt_2. However, the innate reactivity in C2-position can be suppressed using a coordinating group that can direct the deprotonation in *meta*, as the same authors have demonstrated in the late-stage functionalisation of quinine **27** (Scheme 25).[40]

In particular, upon deprotonation of the free alcohol with MeLi and activation of the pyridine with BF_3, the deprotonation with the bulky base occurs selectively at the *meta*-position due to the stabilizing coordination of the quinuclidine nitrogen to the magnesium atom. Subsequent quenching with a bromo-based electrophile gave product **100** in 66% yield. Other electrophiles such as allyl bromide and iodine could also be used in this process. Moreover, the magnesiated pyridine **27**-Mg could be engaged in a Pd-catalyzed Negishi cross-coupling with aryl iodides upon treatment with zinc dichloride (product **103**). It has to be noted that the protection of the free alcohol with a TBDMS group prevented the stabilising interaction (due to steric hindrance), thus restoring the innate deprotonation in C2-position (as seen in section 2.2). While *meta*-deprotonations are highly appealing to introduce a variety of functionalisations, the need for a directing group and the potential incompatibility with other susceptible functional groups limits somehow the applicability of this protocol for LSF.



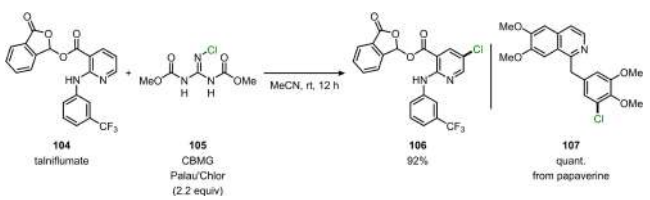
Scheme 25. *meta*-Functionalisation of quinine.

3.3. *meta*-Electrophilic aromatic substitutions

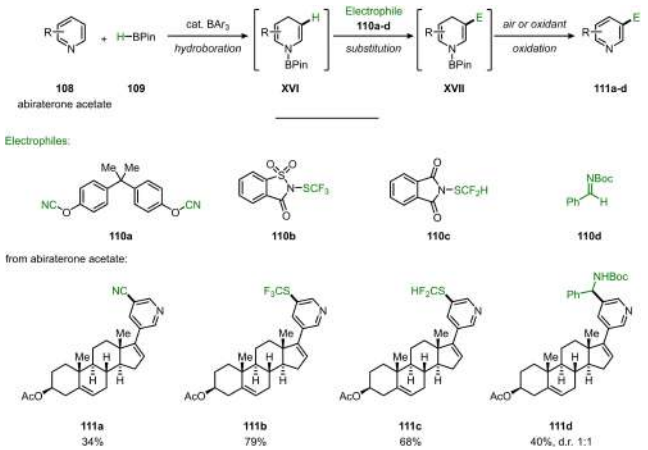
Pyridines are usually poorly reactive in Electrophilic Aromatic Substitution (S_EAr) reactions owing to the decreased electron density in the aromatic system. However, the introduction of electron-donating substituents and the use of highly reactive electrophilic partners could overcome the limited reactivity. A rare example of this strategy was reported by Baran and co-workers when developing novel and reactive chlorinating reagents (Scheme 26). The authors found that treatment of the anti-inflammatory drug talniflumate **104** with chlorobis(methoxycarbonyl)guanidine **105** (Palau'chlor) provided the corresponding *meta*-chlorinated product **106** in 92% yield.[54] Interestingly, no chlorination on the other aromatic rings was observed. The reaction is very appealing considering the mild reaction conditions and the fact that Palau'chlor is now commercially available. However, this strategy seems limited to the chlorination of 2-aminopyridine derivatives since non-activated pyridines, 2-hydroxypridine, and 2-(tert-butoxy)pyridine were not reactive substrates under the same reaction conditions, whereas opium alkaloid papaverine **107** gave chlorination only on the more electron-rich benzyl ring. Nevertheless, despite this limitation, the possibility to extend this approach to other reactive electrophiles could open new possibilities in late-stage functionalisation of 2-aminopyridines.

3.4. *meta*-Functionalisations *via* dearomatisation strategies

An appealing strategy for *meta*-functionalisations exploits the temporary dearomatisation of the pyridine ring to give an electron-rich enamine. This intermediate is then reacted with an electrophile, and, upon rearomatisation, a *meta*-substituted pyridine is obtained. This strategy exploiting the temporary dearomatisation of pyridines has been used to achieve *meta*-regioselectivity, as successfully reported by Wang and co-workers in the late-stage functionalisation of abiraterone acetate **108**, a corticosteroid for prostate cancer (Scheme 27).[55–57] In this case, a borane-catalysed 1,4-hydroboration of the pyridine ring with HBpin **109** yielded enamine **XVI** which is then reacted with an electrophile in *meta*-position. The corresponding intermediate **XVII** is then aromatised using an oxidant. Notably, during the cyanation, aromatisation of the 1,4-dihydropyridine back to the starting material could occur, thus the cyano source **110a** (that is also an oxidant) with a low reduction potential was chosen to minimise the competing oxidation reaction.



Scheme 26. *meta*-Chlorination of talniflumate.

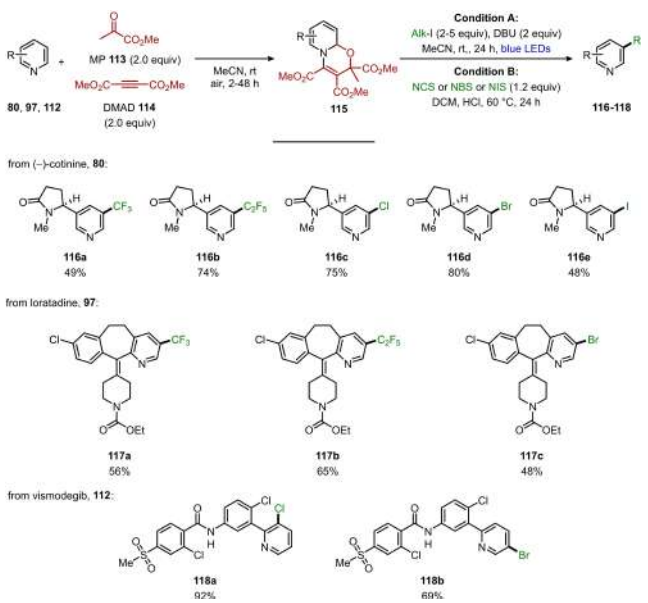


Scheme 27. Abiraterone acetate functionalisation via enamine intermediate.

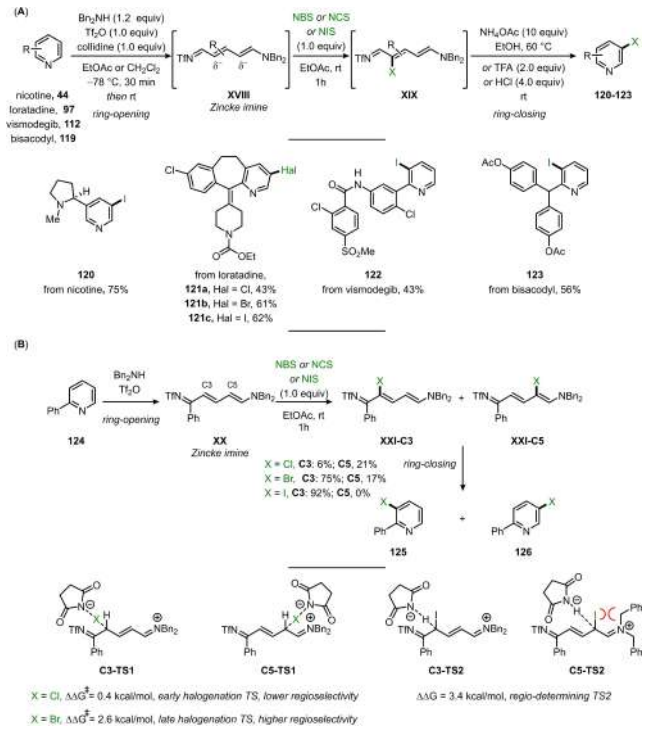
Following Wang's reductive dearomatisation strategies, recently Studer and co-workers have implemented a redox-neutral approach which could be applied to several bioactive molecules, including (−)-cotinine **80**, loratadine **97** and anti-cancer agent vismodegib **112** (Scheme 28).[58] In the first step, the pyridine ring is converted into an oxazino pyridine **115** via dearomative cycloaddition between Huisgen 1,4-dipoles, formed upon treatment with dimethyl acetylenedicarboxylate **114**, and methyl pyruvate **113**.

The oxazino pyridine **115** was stable toward air, water, and silica-gel-column chromatography; moreover, it could be used as mixtures of diastereoisomers since they all converged to the same final product. In the second step, regioselective radical addition, followed by acid-promoted rearomatisation provided the desired products **116**–**118**. It is important to note that a variety of radical precursors or electrophilic reagents could be used in the *meta*-functionalisation step, as demonstrated by the synthesis of perfluoroalkyl, chloro, bromo, iodo, nitro, thio, and seleno *N*-heteroarenes. Interestingly, among the halogen series, a switch in *meta*-regioselectivity was observed going from chlorination to bromination/iodination, as highlighted in the case of vismodegib derivatives **118a**–**b**. A plausible explanation is that chlorination occurs irreversibly at the more nucleophilic C3-position, whereas a reversible bromination leads to the less sterically hindered C5-bromo oxazino pyridine intermediate. The wide range of functionalisations achievable, along with the possibility to perform this chemistry in gram-scale without an inert atmosphere, makes this strategy an appealing tool for LSF of *N*-heterocyclic drugs.

The strategies reported so far involved the direct installation of a novel functionality on the pyridine ring. An alternative approach involves instead a reaction sequence of pyridyl ring opening, functionalisation, and pyridyl ring-closing, as recently reported by McNally and co-workers in their late-stage halogenation of complex pyridines such as nicotine **44**, loratadine **97**, vismodegib **112** and laxative drug bisacodyl **119** (Scheme 29A).[59] This protocol uses a modified version of the classic Zincke ring-opening reaction[60] where, upon treatment of pyridines with triflic anhydride and a secondary amine, azatrienes **XVIII** ("Zincke imines") are obtained. These intermediates are polarized alkenes that undergo electrophilic substitution reactions. The authors exploited this reactivity to selectively halogenate the Zincke imines in C3-position, using *N*-halosuccinimides as the source of the electrophilic halogen. The



Scheme 28. Pyridine *meta*-functionalisations via oxazino pyridines.



Scheme 29. (A) *meta*-Halogenation via Zincke intermediates; (B) Regioselectivity rationale for 2-substituted pyridines.

halogenated azatrienes **XIX** are then reconverted in the corresponding pyridines **120**–**123** by treatment with NH_4OAc or trifluoroacetic acid or HCl. Despite the invasive nature of the ring-opening reactions, the protocol is compatible with late-stage functionalisations, as the authors demonstrated for complex structures of pharmaceutical interest. It is important to note that, in presence of a substituent at position C2, the nature of the halogen electrophile could impact the preference for the C3-position over the analogue C5 (Scheme 29B). For instance, computational studies for the halogenation of 2-phenyl pyridine **124** indicated that in chlorination/bromination reactions the selectivity-determining step is the addition of the electrophiles via the transition state **TS1**. In the bromination, this step proceeds through a later transition state therefore, for the Hammond postulate, a larger difference in energy between the corresponding **C3-TS1** and **C5-TS1** is expected as the result of a more stable developing α,β-unsaturated iminium ion. By contrast, in the chlorination **TS1** has an early transition-state character with minimal discrimination between **C3-TS1** and **C5-TS1**, thus causing lower regioselectivity. In the iodination, the addition of the electrophiles is now reversible, thus the subsequent deprotonation, proceeding via **TS2**, is the rate- and selectivity-determining step. This step dictates the regioselectivity since restoring planarity in the corresponding **C5-TS2** results in increased $A^{1,3}$ strain between the enamine carbon substituent and the iodide (not observed in **C3-TS2**).

The selective *meta*-halogenation of pyridines developed by the McNally group is remarkable also in terms of chemoselectivity, as demonstrated by the absence of halogenation in the other aromatic rings of bisacodyl **119**. Indeed, exclusive pyridine halogenation is observed even for pyridines containing electron-rich rings such as anisole, thiophenes, furans, and phenoxy groups. The regio- and chemoselectivity of this protocol, along with the possibility to perform it in one-pot, renders this strategy a valuable tool in the late-stage halogenation of pyridine-containing drugs, especially when the installed halogen becomes a useful handle for further derivatisation.

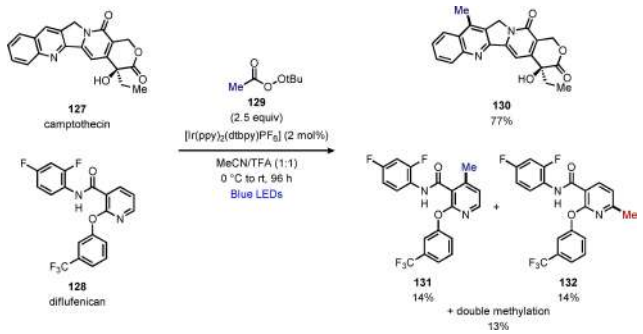
4. *para*-Selective LSF

As for the *ortho*-position, LSF at the *para*-position exploits the innate electrophilic character of this carbon, especially for the addition of radical species. However, LSF at the C2-position seems to be predominant, thus C4-functionalisation is usually achieved by sterically encumbering the *ortho*-position.

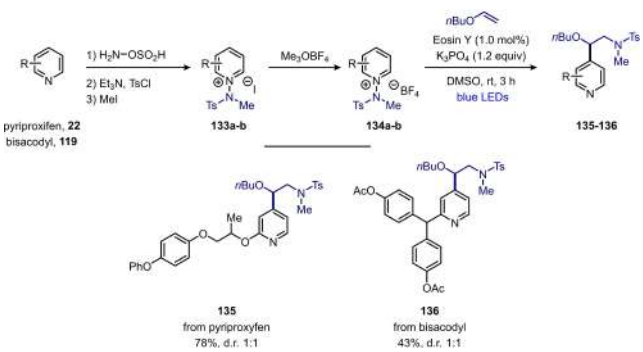
4.1. *para*-Addition of radicals

As seen in section 2.1, Minisci-type reactions, especially under mild conditions, are efficient ways for late-stage functionalisations of elaborated pyridines. Carbon-centered radicals can be generated from different precursors, yet small alkyl radicals (such as a methyl group) are usually hard to generate due to their instability. Considering that a methyl group can impact the pharmacokinetic profile of bioactive compounds ("magic methyl"),[61] several strategies have been put forward to address this limitation in Minisci-type chemistry. One of them, successful also in LSF, has been reported by DiRocco and co-workers in their methylation of camptothecin **127**, a topoisomerase inhibitor alkaloid (Scheme 30).[62] The use of *tert*-butylperacetate **129** as radical precursors was strategic since, upon reduction by the excited photocatalyst, it released a *tert*-butoxy radical from which a *beta*-scission generate the desired methyl radical, along with the side product acetone.[63] The *para*-selectivity was achieved by blocking the *ortho*-positions, as a regioisomeric C2/C4-mixture **131**–**132** was obtained in the case of the herbicide diflufenican **128**.

Pyridine *N*-oxide are valuable starting materials for polar Reissert-Henze reactions, as highlighted in section 2.3. The corresponding *N*-alkoxypyridinium salts have been used in radical reactions too.[64] Recently, *N*-aminopyridinium salts have emerged as versatile and bench-stable pyridine surrogates which can engage in radical reactions with alkenes.[65] An elegant application of these reagents has been reported by Hong and co-workers in their late-stage alkylation of pyriproxyfen **22** and bisacodyl **119** (Scheme 31).[66] First, the pyridine was *N*-aminated using hydroxylamine-*O*-sulfonic acid or *O*-mesitylsulfonylhydroxylamine. Then, the *N*-aminopyridinium salt was sequentially *N*-tosylated and *N*-methylated using tosyl chloride/Et_3N and methyl iodide to give **133**. Salt metathesis with trimethyloxonium tetrafluoroborate gave *N*-aminopyridinium salt **134**, which was thus used as the reactant in the Eosin Y-photocatalysed radical addition to *n*-butylvinylether. Notably,



Scheme 30. Radical methylation of camptothecin and diflufenican.



Scheme 31. Radical alkylation of *N*-aminopyridinium salts.

134 served as a bifunctional reagent providing the amidyl radical and the pyridyl radical which both added to the olefin. In this case, the high *para*-selectivity was attributed to an electrostatic interaction between the pyridinium nitrogen and sulfonyl group of the β-amino radical, as elucidated by Density Functional Theory. Exploiting the reactivity of *N*-aminopyridinium salts, Hong and co-workers expanded this chemistry to reactions with other coupling partners such as strained bicyclo[1.1.1]pentane, sulfinates, and radical deriving from abundant hydrocarbon feedstocks.[67–69]

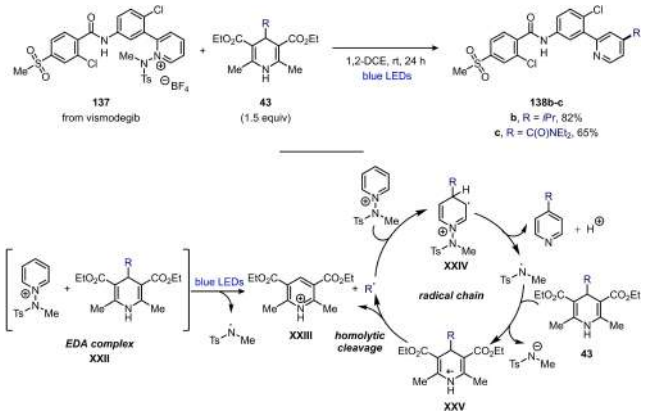
Despite *N*-aminopyridinium salts **133** need to be prepared in a couple of steps, their use is not limited in intramolecular reactions, as the same authors have reported in the late-stage functionalisation of vismodegib **112** (Scheme 32).[70] In this case, no photocatalyst is required since radical generation occurs via an electron donor-acceptor (EDA) complex **XXII** between the Lewis acidic *N*-aminopyridinium salt and the Lewis basic 1,4-dihydropyridine, under visible light irradiation.[71] As seen in section 2.1, DHP **43** is an alkyl or carbamoyl radical precursor, whereas the amido group at the pyridinium salt plays multiple roles as a radical chain propagator, base, and regioselectivity inducer. Indeed, a higher energy barrier was calculated for the *ortho*-addition, probably due to the steric congestion around the C2-position by the nearby amido group of the pyridinium salt.

While DHPs need to be synthesised, the use of more available radical precursors (e.g. alkyl bromides) has been investigated, too.[72] In this regard, it has been shown that alcohols and thiols can act as alkyl radical precursors in photoredox catalysis.[73–75] This has been exploited again by the Hong group in their late-stage alkylation of vismodegib **112** (Scheme 33).[76]

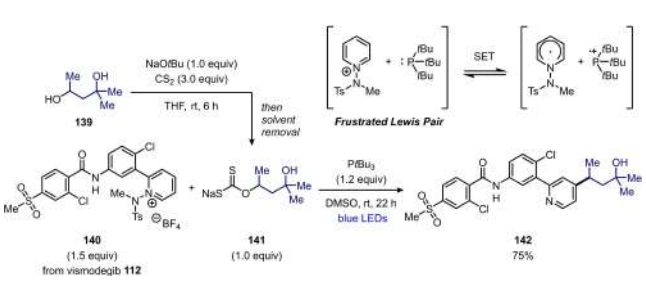
In this case, the *N*-aminopyridinium salt **140** forms an EDA complex with the stoichiometric added P*t*Bu$_3$, whereas the alkyl radical derives from the in situ conversion of the alcohol **139** to the corresponding xanthane **141** using CS_2 and a base. Importantly, these radicals cannot be obtained under standard Minisci conditions since requiring an acidic environment. As for the examples above, no *ortho*-addition was observed probably due the shielding provided by the nearby amido group of the pyridinium salt. Notably, visible light irradiation was not needed for the radical generation from the EDA complex (*via* a SET mechanism), although its use accelerated the reaction *via* alternative chain propagation pathways. Moreover, P*t*Bu$_3$ resulted to be the ideal phosphine since, despite being a good single-electron donor, the steric hindrance of the *t*Bu groups limited the nucleophilic attack of this phosphine to the *N*-aminopyridinium salt, thus preventing pyridination of P*t*Bu$_3$ (see below). The use of *N*-aminopyridinium salts in EDA complexes has been recently expanded by the same authors in their *para*-selective borylation of bisacodyl **119** via *N*-aminopyridinium salt **143** (Scheme 34).[77] They used amine- or phosphite-borane adducts **144**–**145** as both the Lewis base component of the EDA complex as well as the borylating agent, in analogy with what reported by Leonori (section 2.1). In contrast to the previous example, visible light irradiation was needed for the EDA complex to undergo a SET process. This methodology represents a rare example of *para*-borylation of elaborated pyridines, with the installed group serving as a handle for further cross coupling reactions (shown for 2-phenylpyridine **148**).

4.2. *para*-Substitution *via* phosphonium chemistry

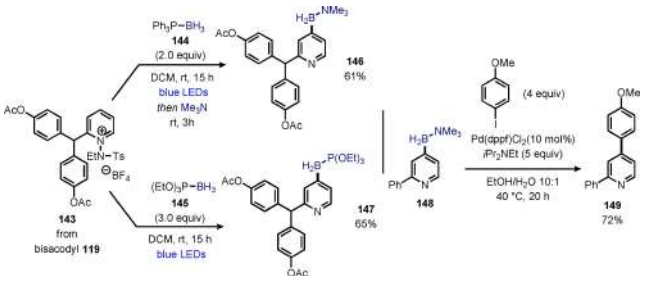
As seen in section 4.1, *N*-aminopyridinium salts and P*t*Bu$_3$ form EDA complexes which can be exploited in the radical functionalisation of pyridines. However, replacing *N*-aminopyridinium salts with *N*-triflyl pyridinium salts, nucleophilic addition of the phosphine at the C4-position is usually observed. Indeed, Anders and co-workers have shown that the sequential addition to pyridine **1** of Tf_2O, Ph_3P and Et_3N yields 4-pyridyl



Scheme 32. Vismodegib alkylation.



Scheme 33. Vismodegib alkylation with xanthates.



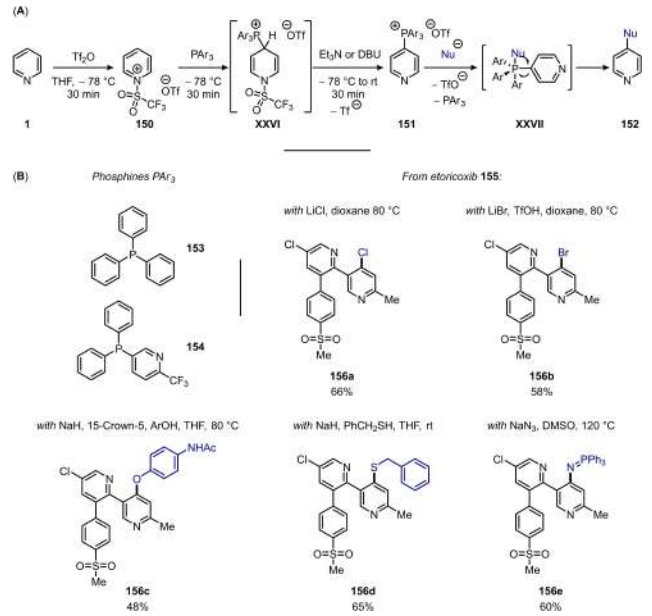
Scheme 34. *para*-Borylation of bisacodyl.

phosphonium triflate **151** in good yields (Scheme 35A).[78] In particular, upon formation of a triflyl salt, attack of the phosphine furnishes a dearomatized intermediate **XXVI** which is then deprotonated to give the corresponding 4-pyridyl phosphonium triflate **151**. The added Ph_3P- group can then be replaced with a nucleophile. This second step involves nucleophilic coordination to the phosphonium to give a phosphorane intermediate **XXVII** from which a ligand-coupling elimination yields the functionalised pyridine. Building on this seminal work, McNally and co-workers have developed a robust research program aimed at the late-stage functionalisation of elaborated pyridines, as demonstrated for etoricoxib **155**, a COX-2 inhibitor (Scheme 35B).[79–83] Notably, this chemistry can be extended to a variety of heteroatomic nucleophiles, including sulphur- and selenium-based ones.[84] Carbon-centered nucleophiles, from carbocycles to fluoromethyl groups, as well as halides, can also be employed, although requiring adjustments to the reaction conditions (e.g. the additional use of transition metals or designed phosphines such as **154**).[85] As for the *N*-aminopyridinium salts, the *para*-selectivity (determined in the first step of the reaction) is attributed to the steric congestion around the *ortho*-position.[86] Notably, tuning of the reaction conditions (e.g. reagents addition) allows also chemoselective *para*-functionalisations of complex substrates containing multiple pyridine rings.[87]

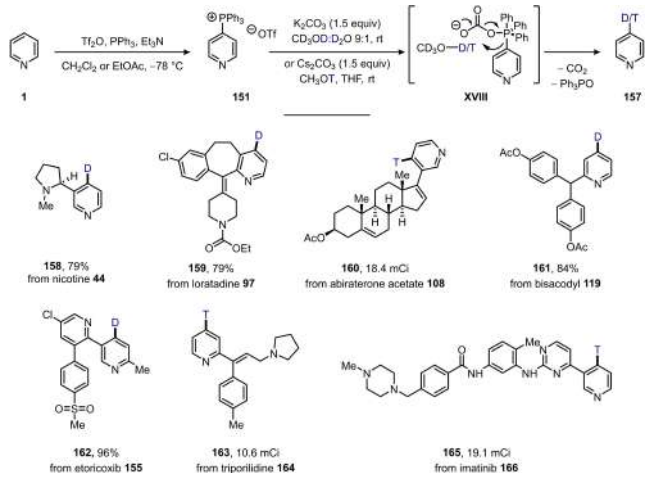
When potassium carbonate was employed as the nucleophile, no ligand-coupling was observed, with the phosphorane intermediate decomposing to CO_2, Ph_3PO and the initial pyridine. This side-reactivity was strategically employed by the McNally group for the *para*-selective deuteration/tritiation of many pharmaceuticals (Scheme 36).[88]

Para-functionalisation via phosphonium chemistry has been exploited also to install a pyridine moiety, thus allowing the synthesis of heterobiaryls, as shown for the antihistamine chlorphenamine **173** and other pyridine-containing drugs (Scheme 37).[89] The mechanism is shown for 2-phenyl pyridine **167**, which is first converted into the corresponding heteroaryl phosphine **169** via intermediates **XXIX–XXX**, exploiting the reactivity of fragmentable phosphine **168**. The heteroaryl phosphine **169** then adds as the nucleophile to the triflyl-activated pyridine of interest. The resulting dipyridyl phosphorane **170** undergoes then a ligand-coupling elimination under acidic conditions to afford the desired bipyridine **171**.

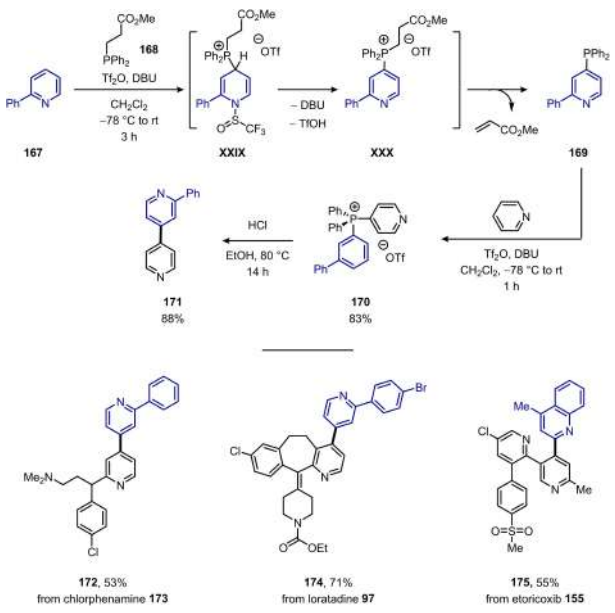
Notably, phosphine addition in both steps is *para*-selective, thus 4,4′-bipyridines are constructed in this way, while for C4-substituted pyridines, *ortho*-selectivity is observed, as for **175**. In conclusion, the easy accessibility of 4-pyridyl phosphonium salts (via simple filtration) and the wide range of compatible



Scheme 35. Etoricoxib functionalisations mediated by phosphines.



Scheme 36. Deauteration and tritiation via 4-pyridyl phosphonium triflates.



Scheme 37. Heterobiaryl synthesis by contractive C–C coupling via P(V) intermediates.

nucleophiles are relevant features for application in late-stage functionalisation, as the authors have repeatedly demonstrated.

5. Examples reported in industrial patents

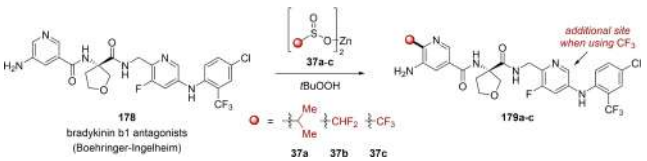
New and more selective late-stage functionalisations are finding applications in industries, especially in the competitive landscape of pharma. In fact, within a medicinal chemistry project, LSF approaches can be used in the earlier *hit-to-lead* phase – to find new exit vectors of a given scaffold – or in the later *lead-optimisation* phase – to optimize the pharmacological bioactivity of lead compounds.[90] In both cases, a chemical transformation can be considered as a useful late-stage functionalisation if it does not require prefunctionalisations.[91] Moreover, a synthetic method, to be widespread in the industry, should be simple to use and employ commercially available reactants/catalysts, thus not all the methodologies described above may be applicable. Instead, the lack of regioselectivity, if coupled with efficient purification techniques available in industries, could be an advantage to simultaneously synthesize products that otherwise would require a longer synthesis or could not be achievable by known synthetic routes.[92] This has been observed in many functionalisations of elaborated pyridines reported by pharmaceutical companies, as collected in this chapter.

A powerful demonstration of late-stage functionalisations has been reported by researchers at Janssen when developing MALT1 inhibitors starting from compound **176** (Scheme 38).[93] Under Minisci-type conditions or using commercially available zinc sulfinates **37**, the authors managed to install a variety of alkyl groups, including a difluoromethyl moiety, in the *ortho*-position of the isoquinoline ring. The regioselectivity here was achieved by blocking the *para*-position since replacing the isoquinoline with a 5-quinolinyl moiety gave a mixture of regioisomeric products (observed for the -CHF_2 radical). It has to be noted that compound **176** contains another pyridine ring, yet the reaction is chemoselective probably due to the difference between the electronic properties of the two rings.

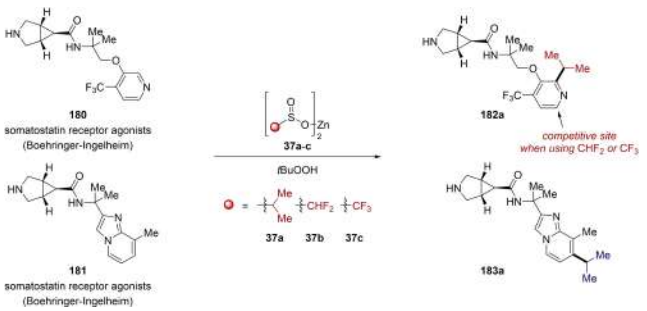
Another interesting example of chemoselective late-stage functionalisations has been reported by researchers at Boehringer-Ingelheim when developing bradykinin b1 antagonists starting from compound **178** (Scheme 39).[94,95] Using zinc sulfinates, the authors managed to selectively install a -*i*Pr group and a –CHF_2 group, whereas the –CF_3 radical gave chemoselectively issues attacking both pyridines. Notably, only *ortho*-functionalisation at the C2-position was observed probably because less sterically hindered than the C5.

Within radical functionalisations, another example reported by the Boehringer-Ingelheim laboratories is the late-stage functionalisation of compounds **180**–**181** when working on somatostatin receptor subtype 4 agonists (Scheme 40).[95,96] While in the first case the *ortho*-regioselectivity was achieved by blocking the C4-position, for compound **181** the *para*-selectivity was obtained optimising the reaction conditions. However, minimal discrimination between the two *ortho*-positions was observed when treating compound **180** with fluoromethyl radicals.

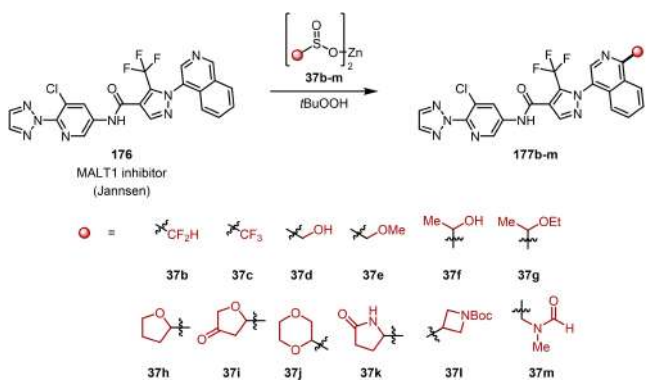
Other examples from the same laboratories include the late-stage functionalisation of triazolylphenyl sulfonamides **184** as a serine/threonine kinase inhibitor (Scheme 41).[97] While selective *ortho*-functionalisation was reported in all cases, the discrimination between the C2- and the C5-position was not observed replacing the methoxy group with amines or in other similar substrates.



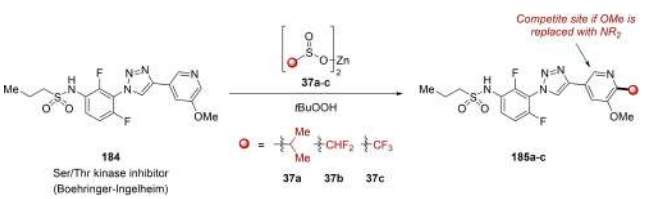
Scheme 39. Bradykinin b1 antagonists functionalisation with zinc sulfinates.



Scheme 40. Somatostatin receptor agonists functionalisation with zinc sulfinates.



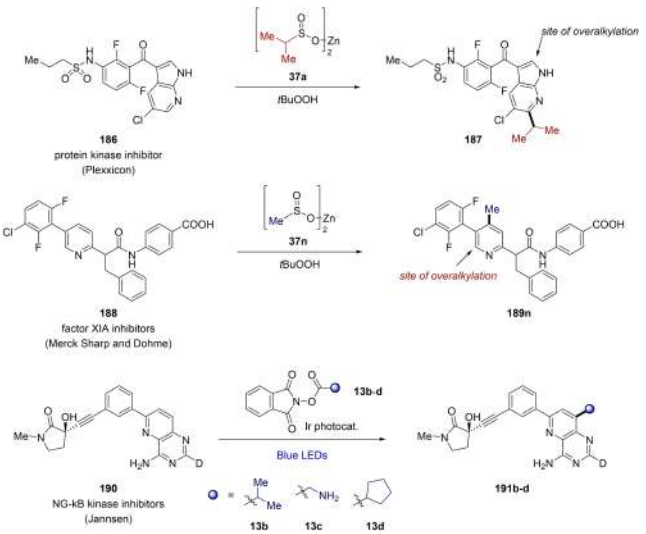
Scheme 38. MALT1 inhibitor functionalisation with zinc sulfinates.



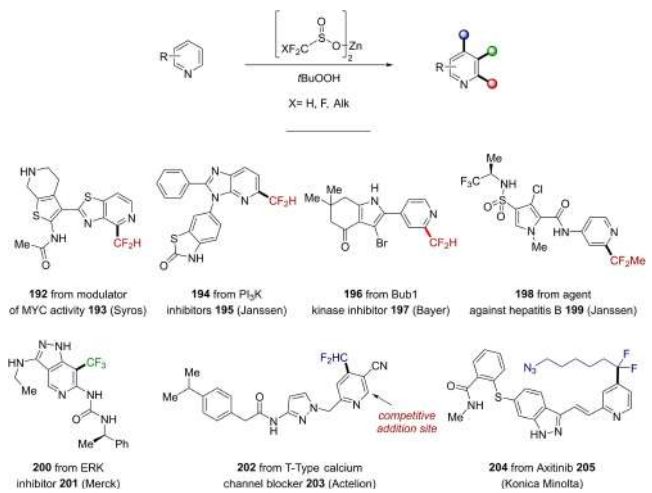
Scheme 41. Ser/Thr kinase inhibitor functionalisation with zinc sulfinates.

Finally, we would like to conclude this section by reporting a series of complex pyridines that have been successfully decorated with alkyl groups (Scheme 42) or fluorine-containing groups (Scheme 43).

For compound **186**, developed by Plexxicon as protein kinase derivatives, the radical *ortho*-functionalisation with zinc sulfinate **35 a** was highly selective, with overalkylation observed not on the pyridine ring but on the pyrrole moiety.[98] Compound **188**, used by Merck Sharp and Dohme corporation as starting block for the development of factor XIA inhibitors, was methylated using the conditions reported in section 2.1, with both *ortho*- and *para*-position being functionalised.[99] Pyridopyrimidine **190** was instead used by Janssen to develop novel inhibitors of NG-kB kinase: using redox activate ester (section 2.1), a small library of para-substituted derivatives was obtained.[100] While the regioselectivity is obvious in this case, the chemoselectivity is interesting since the pyrimidine could also have reacted at the C2-position, thus losing the incorporated deuterium-atom.[101] No activation of the pyrimidine ring was observed in the late-stage functionalisation of Imatinib using redox active esters, as reported by Bristol-Myers Squibb.[102] Nevertheless, the regioselective on the pyridine ring was quite poor, yielding a mixture of mono alkylated and dialkylated regioisomers.



Scheme 42. Radical alkylation of pyridines **186**, **188**, **190**.



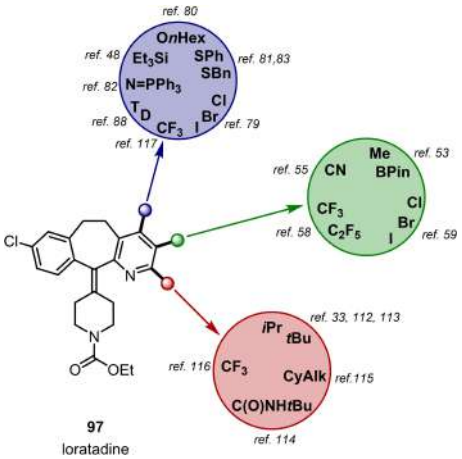
Scheme 43. Radical fluoroalkylation of pyridines **193**–**205**.

Using zinc difluoromethanesulfinate, compound **193**, developed by Syros Pharmaceuticals as a modulator of MYC activity, was successfully *ortho*-difluoromethylated.[103] Similar results were obtained for compound **195**, also containing a fused pyridine ring, as reported by scientists at Janssen during the development of PI3K inhibitors.[104] Under similar reaction conditions, bub1 inhibitor 1 **197** gave the corresponding product **196**.[105] Other industrial applications of radical fluoromethylations using the corresponding zinc sulfinates have been reported for compound **199** (as agent against hepatitis B) and compound **201** (an ERK inhibitor developed by Merck).[106,107] Notably, given the electrophilic nature of the -CF_3 radical, **201** was functionalised in *meta*-position which is the most nucleophilic site of the aminopyridine moiety. Compound **203** gave a mixture of C2/C4-regioisomers, with both products showing biological activity as T-Type calcium channel blockers.[108] Axitinib **205** (Konica Minolta) was fluoroalkylated using zinc sulfinate, although poor regioselectivity was observed in the last case.[109]

6. Conclusions and Outlook

Late-stage functionalisations of intricate structures have lately become affordable due to significant progress in organic synthesis, specifically through the progress in chemoselective methods that can accommodate a broad range of functional groups. When it comes to *N*-heterocycles, different strategies have been developed for the late-stage functionalisation of complex natural products or drugs containing the pyridine moiety. To give an overview of the regioselective LSF methods available for pyridines, we selected the antihistamine loratadine **97** as the prototypical pyridine drug (Scheme 44). Loratadine not only offers three sites exploitable as vectors for derivatisation, but also represents a benchmark for new method developments, and a test for regioselective reactions. For each position (*ortho*, *meta* and *para*), we highlighted the functional groups which can be installed using known regioselective methods. The overview of methods available for loratadine allows us to draw some conclusions on the LSF of pyridine-containing bioactive molecules. Overall, the most common approach is the *ortho*-functionalisation with radicals (Minisci-type chemistry), thus exploiting the innate electrophilic character of this carbon.

The survey of patent literature highlights the predominance of zinc sulfinates as radical precursors. Indeed, their commercial availability and the practical reaction conditions for radical generation made them appealing to medicinal chemists. The electrophilicity of pyridine *ortho*-position also allows deprotonation or oxidation at this site, two other strategies reported in LSF of pyridine-containing drugs. These approaches allow the introduction of heteroatoms (halogens, pnictogens) in the



Scheme 44. Loratadine as a platform for late-stage pyridine functionalisation.

ortho-position, thus complementary to the Minisci reaction which exploits carbon-based radicals. The *meta*-functionalisation is by far the hardest to achieve on drug-like molecules since it must be guided by a directing group or by sterics. Alternatively, if the parent drug contains a 2-aminopyridine moiety, then an electrophilic aromatic substitution could be exploited employing a reactive electrophilic coupling partner, as reported for Talniflumate **104**. More recently, strategies based on the Zincke enamine have emerged, and they augur well for the future development of more practical *meta*-functionalisations. *Para*-functionalisation is usually achieved by exploiting the innate electrophilic character of this carbon, especially for the addition of radical species. The use of *N*-aminopyridinium salts allows highly selective *para*-addition of radicals, thanks to the steric congestion around the C2-position by the nearby amido group of the pyridinium salt. On the other hand, phosphonium chemistry represents nowadays the most attractive alternative to Minisci reactions for the *para*-LSF of pyridine-containing drugs. This recent methodology not only guarantees excellent regioselectivity but also enables the installation of a plethora of functionalities that are difficult to install otherwise. We expect medicinal chemists in industries will soon take advantage of phosphonium chemistry for the diversification of pyridine-containing drugs. In terms of future directions, the paucity of transition metal-catalysed strategies for LSF of pyridine-containing drugs gives the opportunity to further developments beyond C–H borylation. Another aspect which deserves more attention is the enantioselective LSF of pyridine-containing drugs. Indeed, the example reported by Phipps (section 2.1) represents a unicum in the area of drug derivatisation via C–C bond formation. Indeed, more frequently, enantiomers are separated by preparative HPLC from their racemates in medicinal chemistry studies.[93] The need of enantioselective methods for LSF could be met by future implementation of biocatalytic strategies, which are still absent from the toolbox of pyridine derivatization. Nonetheless, recent development augurs well for the use of enzymes in late-stage functionalization of drugs and natural products.[110]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Functionalisation · Late-stage · N-heterocycle · Pyridines · Selectivity

[1] T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245–261.
[2] R. Jana, H. M. Begam, E. Dinda, *Chem. Commun.* **2021**, *57*, 10842–10866.
[3] L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Chem. Rev.* **2021**, *5*, 522–545.
[4] L. Zhang, T. Ritter, *J. Am. Chem. Soc.* **2022**, *144*, 2399–2414.
[5] R. Cannalire, S. Pelliccia, L. Sancineto, E. Novellino, G. C. Tron, M. Giustiniano, *Chem. Soc. Rev.* **2021**, *50*, 766–897.
[6] S. K. Parida, S. K. Hota, R. Kumar, S. Murarka, *Chem. Asian J.* **2021**, *16*, 879–889.
[7] S. K. Hota, D. Jinan, S. P. Panda, R. Pan, B. Sahoo, S. Murarka, *Asian J. Org. Chem.* **2021**, *10*, 1848–1860.
[8] C. B. Kelly, R. Padilla-Salinas, *Chem. Sci.* **2020**, *11*, 10047–10060.
[9] C. A. Kuttruff, M. Haile, J. Kraml, C. S. Tautermann, *ChemMedChem* **2018**, *13*, 983–987.
[10] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.
[11] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576.
[12] E. Vitaku, D. T. Smith, J. T, Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[13] Y. Ling, Z.-Y. Hao, D. Liang, C.-L. Zhang, Y.-F. Liu, Y. Wang, *Drug Des. Dev. Ther.* **2021**, *15*, 4289–4338.
[14] J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642–2713.
[15] J. Jurczyk, J. Woo, S. F. Kim, B. D. Dherange, R. Sarpong, M. D. Levin, *Nat. Synth.* **2022**, *1*, 352–364.
[16] F. Minisci, R. Bernardi, F. Bertini, R. Galli, *Tetrahedron* **1971**, *27*, 3575–3579.
[17] F. Minisci, E. Vismara, S. Levi, C. Giordano, *J. Org. Chem.* **1986**, *51*, 536–537.
[18] F. Minisci, A. Citterio, E. Vismara, C. Giordano, *Tetrahedron* **1985**, *41*, 4157–4170.
[19] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80.
[20] J. Jin, D. W. C. MacMillan, *Nature* **2015**, *525*, 87–90.
[21] W. M. Cheng, R. Shang, Y. Fu, *ACS Catal.* **2017**, *7*, 907–911.
[22] R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2008**, *360*, 419–422.
[23] C. A. Huff, R. D. Cohen, K. D. Dykstra, E. Streckfuss, D. A. DiRocco, S. W. Krska, *J. Org. Chem.* **2016**, *81*, 6980–6987.
[24] P. Nuhant, M. S. Oderinde, J. Genovino, A. Juneau, Y. Gagné, C. Allais, G. M. Chinigo, C. Choi, N. W. Sach, L. Bernier, Y. M. Fobian, M. W. Bundesmann, B. Khunte, M. Frenette, O. O. Fadeyi, *Angew. Chem. Int. Ed.* **2017**, *56*, 15309–15313; *Angew. Chem.* **2017**, *129*, 15511–15515.
[25] J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113.

[26] D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688–6699.
[27] J. Jeon, Y. He, S. Shin, S. Hong, *Angew. Chem. Int. Ed.* **2020**, *59*, 281–285; *Angew. Chem.* **2020**, *132*, 287–291.
[28] Y. Moon, W. Lee, S. Hong, *J. Am. Chem. Soc.* **2020**, *142*, 12420–12429.
[29] S. Fukuzumi, K. Ohkubo, *Org. Biomol. Chem.* **2014**, *12*, 6059–6071.
[30] J. K. Matsui, D. N. Primer, G. A. Molander, *Chem. Sci.* **2017**, *8*, 3512–3522.
[31] J. H. Kim, T. Constantin, M. Simonetti, J. Llaveria, N. S. Sheikh, D. Leonori, *Nature* **2021**, *595*, 677–683.
[32] X. L. Lai, X. M. Shu, J. Song, H. C. Xu, *Angew. Chem. Int. Ed.* **2020**, *59*, 10626–10632; *Angew. Chem.* **2020**, *132*, 10713–10719.
[33] K. Wang, X. Liu, S. Yang, Y. Tian, M. Zhou, J. Zhou, X. Jia, B. Li, S. Liu, J. Chen, *Org. Lett.* **2022**, *24*, 3471–3476.
[34] J. M. Smith, J. A. Dixon, J. N. deGruyter, P. S. Baran, *J. Med. Chem.* **2019**, *62*, 2256–2264.
[35] F. O'Hara, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122–12134.
[36] L. Buzzetti, A. Prieto, S. R. Roy, P. Melchiorre, *Angew. Chem. Int. Ed.* **2017**, *56*, 15039–15043; *Angew. Chem.* **2017**, *129*, 15235–15239.
[37] Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui, G. A. Molander, *J. Am. Chem. Soc.* **2017**, *139*, 12251–12258.
[38] I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196.
[39] E. Le Saux, E. Georgiou, I. A. Dmitriev, W. C. Hartley, P. Melchiorre, *J. Am. Chem. Soc.* **2023**, *145*, 47–52.
[40] M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306–2309.
[41] W. E. McEwen, R. L. Cobb, *Chem. Rev.* **1955**, *55*, 511–549.
[42] S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate, P. S. Baran, *Org. Lett.* **2013**, *15*, 792–795.
[43] P. S. Fier, S. Kim, R. D. Cohen, *J. Am. Chem. Soc.* **2020**, *142*, 8614–8618.
[44] C. K. Mcgill, A. Rappa, *Adv. Heterocycl. Chem.* **1988**, *44*, 1–79.
[45] C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2006**, *45*, 6024–6028; *Angew. Chem.* **2006**, *118*, 6170–6175.
[46] P. S. Fier, J. F. Hartwig, *Science* **2013**, *342*, 956–960.
[47] P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 10139–10147.
[48] Y. Gu, Y. Shen, C. Zarate, R. Martin, *J. Am. Chem. Soc.* **2019**, *141*, 127–132.
[49] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.
[50] M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299.
[51] H. R. Campello, T. Gallagher, *J. Org. Chem.* **2018**, *83*, 516–520.
[52] D. F. Fischer, R. Sarpong, *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927.
[53] Z.-T. He, H. Li, A. M. Haydl, G. T. Whiteker, J. F. Hartwig, *J. Am. Chem. Soc.* **2018**, *140*, 17197–17202.
[54] R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 6908–6911.
[55] M. Zhang, Q. Zhou, H. Luo, Z.-L. Tang, X. Xu, X.-C. Wang, *Angew. Chem. Int. Ed.* **2023**, e202216894.
[56] X.-Y. Zhou, M. Zhang, Z. Liu, J.-H. He, X.-C. Wang, *J. Am. Chem. Soc.* **2022**, *144*, 14463–14470.
[57] Z. Liu, J.-H. He, M. Zhang, Z.-J. Shi, H. Tang, X.-Y. Zhou, J.-J. Tian, X.-C. Wang, *J. Am. Chem. Soc.* **2022**, *144*, 4810–4818.
[58] H. Cao, Q. Cheng, A. Studer, *Science* **2022**, *378*, 779–785.
[59] B. T. Boyle, J. N. Levy, L. de Lescure, R. S. Paton, A. McNally, *Science* **2022**, *378*, 773–779.
[60] C. D. Vanderwal, *J. Org. Chem.* **2011**, *76*, 9555–9567.
[61] D. Aynetdinova, M. C. Callens, H. B. Hicks, C. Y. X. Poh, B. D. A. Shennan, A. M. Boyd, Z. H. Lim, J. A. Leitch, D. J. Dixon, *Chem. Soc. Rev.* **2021**, *50*, 5517–5563.
[62] D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge . *Angew. Chem. Int. Ed.* **2014**, *53*, 4802–4806; *Angew. Chem.* **2014**, *126*, 4902–4906.
[63] M. F. Zady, J. L. Wong, *J. Am. Chem. Soc.* **1977**, *99*, 5096–5101.
[64] F.-S. He, S. Ye, J. Wu, *ACS Catal.* **2019**, *9*, 8943–8960.
[65] T. M. Monos, R. C. McAtee, C. R. J. Stephenson, *Science* **2018**, *361*, 1369–1373.
[66] Y. Moon, B. Park, I. Kim, G. Kang, S. Shin, D. Kang, M.-H. Baik, S. Hong, *Nat. Commun.* **2019**, *10*, 4117.
[67] S. Shin, S. Lee, W. Choi, N. Kim, S. Hong, *Angew. Chem. Int. Ed.* **2021**, *60*, 7873–7879; *Angew. Chem.* **2021**, *133*, 7952–7958.
[68] M. Kim, E. You, S. Park, S. Hong, *Chem. Sci.* **2021**, *12*, 6629–6637.
[69] W. Lee, S. Jung, M. Kim, S. Hong, *J. Am. Chem. Soc.* **2021**, *143*, 3003–3012.
[70] I. Kim, S. Park, S. Hong, *Org. Lett.* **2020**, *22*, 8730–8734.
[71] G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, *J. Am. Chem. Soc.* **2020**, *142*, 5461–5476.
[72] S. Jung, S. Shin, S. Park, S. Hong, *J. Am. Chem. Soc.* **2020**, *142*, 11370–11375.
[73] L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.
[74] C. C. Nawrat, C. R. Jamison, Y. Slutskyy, D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
[75] J. Wu, R. M. Bär, L. Guo, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2019**, *58*, 18830–18834; *Angew. Chem.* **2019**, *131*, 19006–19010.
[76] C.-Y. Tan, M. Kim, I. Park, Y. Kim, S. Hong, *Angew. Chem. Int. Ed.* **2022**, *61*, e202213857.
[77] W. Choi, M. Kim, K. Lee, S. Park, S. Hong, *Org. Lett.* **2022**, *24*, 9452–9457.
[78] E. Anders, F. Markus, *Tetrahedron Lett.* **1987**, *28*, 2675–2676.
[79] J. N. Levy, J. V. Alegre-Requena, R. Liu, R. S. Paton, A. McNally, *J. Am. Chem. Soc.* **2020**, *142*, 11295–11305.
[80] M. C. Hilton, R. D. Dolewski, A. McNally, *J. Am. Chem. Soc.* **2016**, *138*, 13806–13809.
[81] R. G. Anderson, B. M. Jett, A. McNally, *Tetrahedron* **2018**, *74*, 3129–3136.
[82] C. Patel, M. Mohnike, M. C. Hilton, A. McNally, *Org. Lett.* **2018**, *20*, 2607–2610.
[83] R. G. Anderson, B. M. Jett, A. McNally, *Angew. Chem. Int. Ed.* **2018**, *57*, 12514–12518; *Angew. Chem.* **2018**, *130*, 12694–12698.
[84] R. D. Dolewski, M. C. Hilton, A. McNally, *Synlett.* **2018**, *29*, 8–14.
[85] X. Zhang, K. G. Nottingham, C. Patel, J. V. Alegre-Requena, J. N. Levy, R. S. Paton, A. McNally, *Nature* **2021**, *594*, 217–222.
[86] P. Du, Y. Yin, D. Shi, K. Mao, Q. Yu, J. Zhao, *Molecules* **2022**, *27*, 5694.
[87] R. D. Dolewski, P. J. Fricke, A. McNally, *J. Am. Chem. Soc.* **2018**, *140*, 8020–8026.
[88] J. L. Koniarczyk, D. Hesk, A. Overgard, I. W. Davies, A. McNally, *J. Am. Chem. Soc.* **2018**, *140*, 1990–1993.
[89] M. C. Hilton, X. Zhang, B. T. Boyle, J. V. Alegre-Requena, R. S. Paton, A. McNally, *Science* **2018**, *362*, 799–804.
[90] P. Ronchi, S. Guariento, D. Pala, D. Pizzirani, C. Fiorelli, P. Bruno, V. Nigroni, M. Biagetti, *Curr. Org. Chem.* **2021**, *25*, 2089–2115.
[91] J. Börgel, T. Ritter, *Chem* **2020**, *6*, 1877–1887.
[92] S. Guariento, M. Biagetti, P. Ronchi, *Future Med. Chem.* **2020**, *13*, 250–265.
[93] T. Lu, B. D. Allison, J. K. Barbay, P. J. Connolly, M. D. Cummings, G. Diels, J. P. Edwards, K. D. Kreutter, U. Philippar, F. Shen, J. W. J. F. Thuring, T. Wu (Janssen), US 170909, **2018**.
[94] N. Hauel, A. Ceci, H. Doods, I. Konetzki, J. Mack, H. Priepke, A. Schuler-Metz, R. Walter, D. Wiedenmayer (Boehringer-Ingelheim), WO-A1 097372, **2010**.
[95] C. A. Kuttruff, M. Haile, J. Kraml, C. S. Tautermann, *ChemMedChem* **2018**, *13*, 983–987.
[96] R. Giovannini, Y. Cui, H. Doods, M. Ferrara, S. Just, R. Kuelzer, L. Lingard, R. Mazzaferro, K. Rudolf (Boehringer-Ingelheim), WO-A1 184275, **2014**.
[97] S. Steurer (Boehringer-Ingelheim), US–A1 0322803, **2012**.
[98] P. N. Ibrahim, D. R. Artis, R. Bremer, G. Habets, S. Mamo, M. Nespi, C. Zhang, J. Zhang, Y. L. Zhu, R. Zuckerman, B. West, Y. Suzuki, J. Tsai, K.-P. Hirth, G. Bollag, W. Spevak, H. Cho, S. Gillette, G. Wu, H. Zhu, S. Shi S. (Plexxicon), WO 002433, **2007**.
[99] W. Liu, S. D. Edmondson, Z. Guo, E. Mertz, A. K. Ogawa, S.-S. So, W. Sun, L. L. Brockunier (Merck Sharp and Dohme corporation), WO-A1 183709, **2015**.
[100] J. Barbay, W. Chai, W. Eccles, M. D. Hack, A. T. Hermann, W. M. Jones, P. J. Krawczuk, A. D. Leabsack, D. J. Pippel, A. R. Rovira, R. L. Wolin, (Janssen), WO-A1 239999, **2020**.
[101] H. Zhao, J. Jin, *Org. Lett.* **2019**, *21*, 6179–6184.
[102] C. T. Sherwood, N. Li, A. N. Yazdani, T. G. M. Dhar, *J. Org. Chem.* **2018**, *83*, 3000–3012.
[103] C. Roberts, Y. Zhang, F. Beaumier, L. Lepissier, J. J. Marineau, P. B. Rahl, K. Sprott, S. Ciblat, B. Sow, R. Larouche-Gauther, L. Berstler (Syros Pharmaceuticals), WO-A1 196910, **2016**.
[104] J. Evarts, J. Kaplan, L. Patel, S. Perreault, B. W. Phillips, G. Phillips, J. A. Treiberg, S. C. Yeung (Janssen), WO-A1 191743, **2015**.
[105] K. Graham, U. Klar, H. Briem, G. Siemeister, U. Monning, J. Balint (Bayer Pharma Aktiengesellschaft), WO-A1 202755, **2016**.
[106] K. Vandyck, G. Y. P. Hachè, S. L. Last, G. Rombouts, W. G. Verschueren, P. J.-M. B. Raboisson (Janssen), WO-A1 118057, **2015**.
[107] K. J. Wilson, D. J. Witter, P. Siliphaivanh, K. Lipfors, D. Sloman, D. Falcone, B. O'Boyle, U. F. Mansoor, J. Lim, J. L. Methot, C. Boyce, L.

Chen, M. H. Daniels, S. Fevrier, X. Huang, R. Kueukulasuriya, L. Tong, W. Zhou, J. Kozlowski, M. M. Maletic, B. A. Shinkre, J. T. Thatai, R. K. Bakshi, G. B. Karunakaran (Merck Sharp and Dohme corporation), WO-A2 052563, **2014**.
[108] R. Siegrist, B. Heidmann, S. Stamm, J. Gatfield, O. Bezencon O. (Actelion Pharmaceuticals), WO-A1 186056, **2015**.
[109] T. Aimiya, N. Furusawa (Konica Minolta), US-A1 0205417, **2017**.
[110] E. Romero, B. S. Jones, B. N. Hogg, A. Rué Casamajo, M. A. Hayes, S. L. Flitsch, N. J. Turner, C. Schnepel, *Angew. Chem. Int. Ed.* **2021**, *60*, 16824–18855; *Angew. Chem.* **2021**, *133*, 16962–16993.
[111] X. A. F. Cook, A. de Gombert, J. McKnight, L. R. E. Pantaine, M. C. Willis, *Angew. Chem. Int. Ed.* **2021**, *60*, 11068–11091; *Angew. Chem.* **2021**, *133*, 11168–11191.
[112] J. Dong, X. Lyu, Z. Wang, X. Wang, H. Song, Y. Liu, Q. Wang, *Chem. Sci.* **2019**, *10*, 976–982.
[113] J. Li, C.-Y. Huang, J.-T. Han, C.-J. Li, *ACS Catal.* **2021** *11*, 14148–14158.
[114] X.-L. Lai, X.-M. Shu, J. Song, H.-C. Xu, *Angew. Chem. Int. Ed.* **2020**, *59*, 10626–10632; *Angew. Chem.* **2020**, *132*, 10713–10719.
[115] J. J. Perkins, J. W. Schubert, E. C. Streckfuss, J. Balsells, A. ElMarrouni, *Eur. J. Org. Chem.* **2020**, *2020,* 1515–1522.
[116] J. Yu, R. Zhan, C.-J. Li, H. Zeng, *Sci. China Chem.* **2023**, *66*, 133–138.
[117] K. Nottingham, C. Patel, J. Levy, A. McNally, X. Zhang, WO-A1 087129, **2022**.

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