Chemistry–A European Journal
Concept
doi.org/10.1002/chem.202004373
Chemistry Europe
European Chemical Societies Publishing

Drug Discovery

Late-Stage C(sp^2)–H Functionalization: A Powerful Toolkit To Arm Natural Products for In Situ Proteome Profiling?

Ying-Jie Lim, Yulong Kuang, Jie Wu,* and Shao Q. Yao*[a]

Abstract: The comprehensive investigation of target interactions from native cellular environments is of paramount importance for natural products and related bioactive compounds in drug discovery and chemical biology. Current chemoproteomic tools, such as in situ proteome profiling can do so effectively, but rely heavily on "tagged" probes that are accessible through traditional organic synthesis at the reactive sites of a compound, which may often be required for target binding. Late-stage functionalization may resolve such limitations by tagging compounds in a single step at biologically inert C–H bonds. Herein, recent advances in late-stage C(sp^2)–H functionalization of (hetero)arenes, which are present in many natural products, are summarized, and new toolkits for more widespread use of such strategies to install natural products with next-generation "minimalist" linkers for in situ proteome profiling are suggested.

Introduction

Natural products (NPs) play a central role in chemistry and drug discovery.[1] Over the years, despite significant advances in NP isolation, characterization, and chemical synthesis, the use of NPs (or similar bioactive compounds) as drugs has continued to be hampered by unresolved issues, such as safety and off-targets, which often lead to clinical failure. For example, in a typical drug development program, in which it takes, on average, 15 years and more than one billion dollars to put a drug on the market (Figure 1 A), the extremely high attrition rate (>90 %) is, in part, caused by a lack of reliable strategies capable of comprehensively identifying all potential targets (on- and off-) of drug candidates in native cellular environments (in situ), prior to time-consuming and costly clinical trials. Target identification of bioactive compounds, which not only improves our understanding of the mode-of-action of a compound, but also allows the detection of potential adverse effects before clinical trials, and therefore, remains the major bottleneck in any drug discovery program.[2] To fill this knowledge gap, scientists, in recent years, have developed various MS-based platforms for large-scale proteome-wide profiling of bioactive compounds under in situ conditions.[3–7] Among them, chemoproteomic strategies based on the use of small-molecule probes derived from bioactive compounds have received much attention (Figure 1 B), owing to their easy operation, high sensitivity, and reliability. Such approaches are now broadly referred to as "in situ proteome profiling," and, in the context of chemical probes derived from drug molecules, they are simply called "in situ drug profiling."[8]

The emergence of in situ drug profiling has coincided with the development of activity-based protein profiling (ABPP) and click chemistry, terms coined by the groups of Cravatt and Sharpless, respectively.[9,10] ABPP uses chemical probes that react irreversibly with mechanistically related classes of enzymes, and therefore, has the ability to monitor enzyme activity rather than abundance.[11] Click chemistry refers to chemical reactions that are selective, modular, wide in scope, and high yielding, and CuAAC between an azide and terminal alkyne, to form 1,2,3-triazole (Figure 1 B), is the most widely used click reaction, to date.[12] The first marriage between ABPP and CuAAC occurred in 2003,[13] helping to popularize the use of small-molecule active-site probes for biological interrogation. This was shown by the development of active-site probes for profiling various biological targets, such as matrix metalloproteases;[14a] bacterial enzymes involved in peptidoglycan assembly;[14b] and protein targets of orlistat™, a United States Food and Drug Administration (FDA)-approved drug to treat obesity and diabetes.[14c] Orlistat is a NP-derived covalent drug containing an electrophilic β-lactone and several aliphatic chains; replacement of a C(sp^3)–C(sp^3) bond with a terminal alkyne thus represents the smallest molecular "surgery" possible, to generate resulting "minimalist" probes capable of recapitulating genuine orlistat–target interaction in situ at the proteome-wide level (Figure 1 B, top).[14c] Because a key requirement of this approach is the formation of covalent probe–target complexes, and most existing drugs (>90 %) on the market are noncovalent drugs, another approach, based on the conversion of transient noncovalent drug–target interactions into isolable, covalent probe–target complexes in situ by using photoaffinity labeling, was reported (Figure 1 B, bottom);[14a,15] this so-called affinity-based protein profiling (*Af*BPP) entails an additional step of functionalizing a noncovalent drug with a PAL, that is,

[a] Dr. Y.-J. Lim, Dr. Y. Kuang, Prof. Dr. J. Wu, Prof. Dr. S. Q. Yao
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
E-mail: chmjie@nus.edu.sg
chmyaosq@nus.edu.sg
The ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202004373.

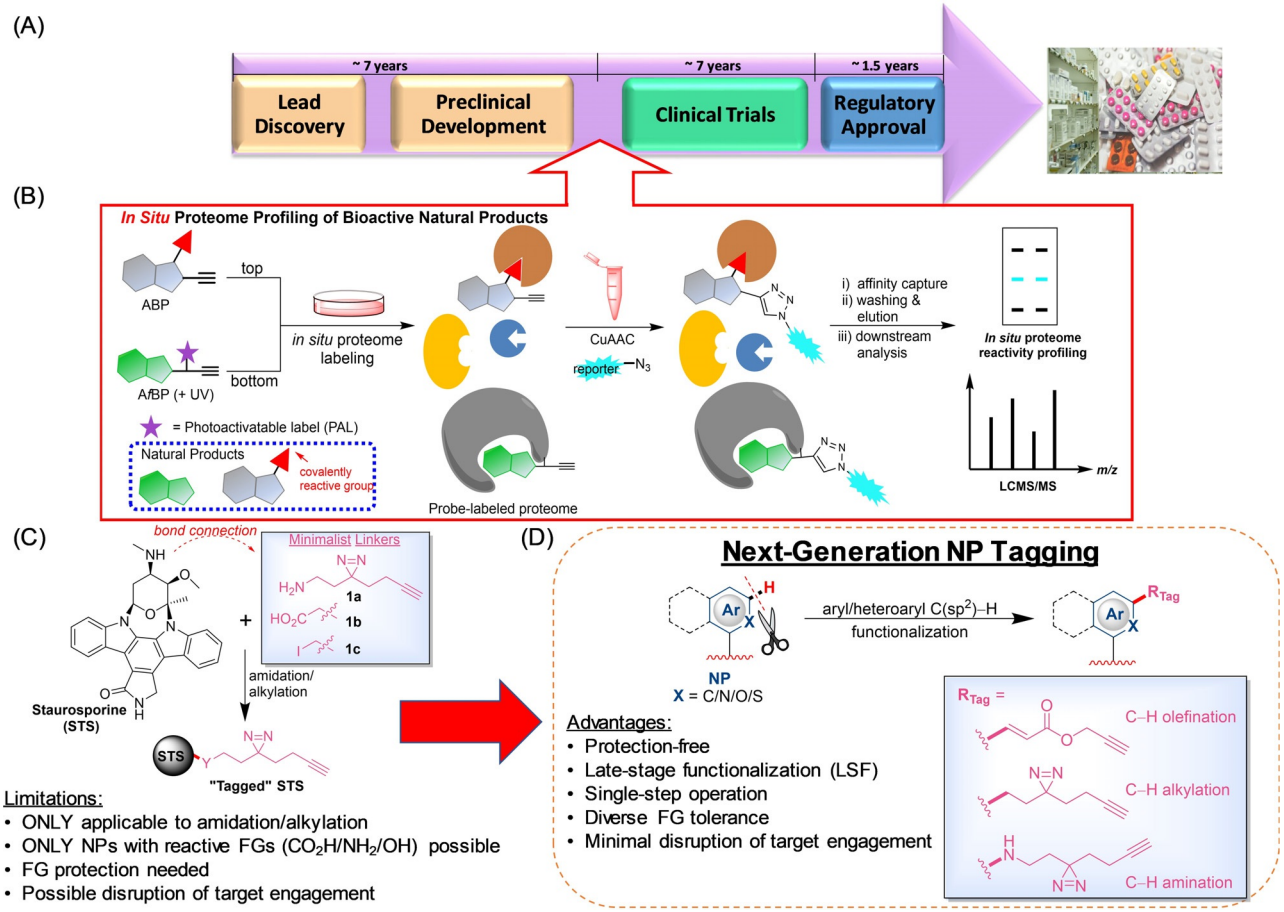

Figure 1. A) Timeline of a typical drug discovery pipeline. B) Steps involved in in situ proteome profiling. Top: An activity-based probe (ABP) containing a "clickable" terminal alkyne generated from a covalent NP. Bottom: An affinity-based probe (*Af*BP) containing a PAL and a terminal alkyne generated from a noncovalent NP. The key principle is to use ABP/*Af*BP to covalently capture probe–target complexes in situ, followed by a Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC) reaction with a suitable reporter (in vitro) and downstream gel- and MS-based analyses.[8] C) Early-generation minimalist linkers developed (boxed), with tagged staurosporine (STS) as an example.[15d] D) Next-generation NP tagging and the corresponding minimalist linkers proposed herein (boxed), based on suitable aryl/heteroaryl $C(sp^2)$–H late-stage functionalization (LSF) chemistries.

an aryl azide, benzophenone, or aryl/alkyl diazirine.[4] For in situ drug profiling, in which structural alteration to a native drug must be kept as small as possible to minimally interfere probe–target binding, the use of minimalist linkers containing a highly compact alkyl diazirine with a terminal alkyne (Figure 1C; **1a–c**),[16] has become popular.[5] These linkers contain an additional functional group (FG), which is normally NH_2, CO_2H, or I, designed to react with FGs (e.g., $CO_2H/NH_2/OH$) available in most bioactive compounds through simple amidation/alkylation reactions. STS, a noncovalent NP with diverse biological activities, could be chemically modified through its secondary amine, in one- to two-step operations, to the yield the corresponding "tagged" STS, which was then used for subsequent in situ proteome profiling (Figure 1B, bottom).[15d] The reliance on classical nucleophilic substitution reactions, however, not only significantly restricts the types of NPs that can be tagged, but also causes possible disruption of probe–target interactions, owing to the often essential role of these FGs in maintaining NP–target binding. Consequently, next-generation NP tagging approaches capable of not only minimalist tagging of a variety of NPs at nonessential sites (preferably in a one-step operation), but also doing so in a protection-free and highly chemo-/regioselective manner, are urgently needed (Figure 1D).

A large number of known NPs contain (hetero)aromatic groups, and aryl/heteroaryl C–H bonds, in many cases, are considered biologically inert.[1] Significant progress has been made in LSF of $C(sp^2)$–H bonds in the last decade alone.[17] The ability to directly functionalize complex NPs through LSF offers great potential in drug discovery and chemical biology, but its adaption by chemical biologists, that is, taking a complex NP to directly "tag" it with a suitable chemical reporter (i.e., fluorophore, affinity label, click label), has lagged behind.[17c] One possible reason is the long-standing challenge to conduct C–H functionalization on structurally complex small molecules in high yields; early-generation LSF chemistries often suffer from harsh reaction conditions, poor FG tolerance, and low reactivity and selectivity.[18] Several ground-breaking discoveries, in recent years, have shown that it is now possible to conduct efficient chemo-/regioselective $C(sp^2)$–H functionalization on complex pharmaceuticals under mild conditions.[17,19] Such examples have already been reviewed extensively.[17] Herein, we

suggest combining LSF of aryl/heteroaryl C(sp^2)–H bonds in NPs with in situ drug profiling, for the first time, by using suitable next-generation minimalist linkers (general structures shown in Figure 1 D, boxed), for both covalent and photoaffinity-based target labeling.[3–5] To keep our discussion within the topic of this Concept, we first briefly summarize recent advances in aryl/heteroaryl C(sp^2)–H LSF that may be directly exploited to introduce the abovementioned next-generation minimalist linkers into NPs and related bioactive compounds.

Modern Aryl C–H Functionalization Methods

Transition-metal-catalyzed aryl/heteroaryl C(sp^2)–H functionalization often requires a directing group (DG) on the aromatic moiety to achieve high regioselectivity, which translates into additional steps for DG installation and removal.[20] Yu et al. recently reported a DG-free C–H olefination on arenes by using simple acrylates as coupling partners at high temperature [Figure 2, Eq. (1)].[21] This method, an extension of well-established Pd^{II} catalysis with mono-*N*-protected amino acids (MPAA) as ligands,[22] was greatly facilitated by the introduction of a novel 2-pyridone ligand (**2** in Figure 2), and applicable for functionalizing diverse arene and heteroarene substrates, with high regioselectivity and good FG tolerance. Moreover, this method was successfully extended for LSF of NPs and drug molecules such as camptothecin and fenofibrate. A recent report by Zhu et al. demonstrated a ligand-free Pd^{II}-catalysis approach, which was applied to *ortho*-olefination of a broad range of unprotected phenols with exclusive regioselectivity [Figure 2, Eq. (2)].[23] This method was shown to have a wide FG tolerance, ranging from diverse carbonyl FGs and nitriles to sulfonyl fluorides, and even a terminal alkyne in one instance. The strategy was subsequently used for LSF of phenol-containing NPs, which are present abundantly in nature (e.g., estrone, estradiol, and ethinylestradiol).

Compared with transition-metal-catalyzed C–H activation, radical reactions display much improved water tolerance.[17a] Their lack of widespread use in NP synthesis had been plagued by difficulties in generating radicals from stable precursors under mild conditions. One classical radical reaction for heteroarenes is the Minisci reaction, which features the generation of alkyl and acyl radicals (normally from carboxylic acids) with strong oxidants.[24] Recent discoveries that use alkyl boronic acids, potassium alkyltrifluoroborates, or metal sulfinates as stable radical precursors have fueled their wide adoption by both academic and industrial laboratories.[25–27] Of particular interest to us are Baran's zinc/sodium sulfinates for heteroarene functionalization in the presence of TBHP [an oxidant; Figure 2, Eq. (3)].[25] This reaction is remarkable in its compatibility with diverse heteroarenes, scalability, and water tolerance.[25a] A recent report from Leonori et al. suggested an alternative approach with alkyl halides as radical precursors under mild conditions.[26] Classical radical formations from halides employ stoichiometric tin reagents, hydrosilanes, or trialkylborane–dioxygen systems.[27] By using alkyl radicals generated through halogen atom transfer (XAT) between halides and α-aminoalkyl radical intermediates derived from single-electron oxidation of hindered amines, the authors showed that a variety of heteroarenes commonly found in bioactive molecules, including caffeine, indoles, azoles, and benzenoids, could be alkylated in moderate to good yields [Figure 2, Eq. (4)].

An alternative DG-free strategy was developed by the group of Ritter, in which thianthrenes, as synthetic linchpins, were used for selective functionalization of arenes [Figure 2, Eq. (5)].[28] Though the installation of a thiathrene on arenes constitutes an additional step, both the exquisite *para*-regioselectivity of this method and the immense FG tolerance, ranging from free alcohols, halogens and triflates to various carbonyl functionalities, makes it highly attractive. The resulting aryl thiathrenium salt could be further diversified into a wide variety of different *para*-functionalized arenes through transition-metal or photoredox catalysis. As further proof of synthetic utility and scope of their method, LSF was successfully demonstrated on a broad range of pharmaceutical molecules, such

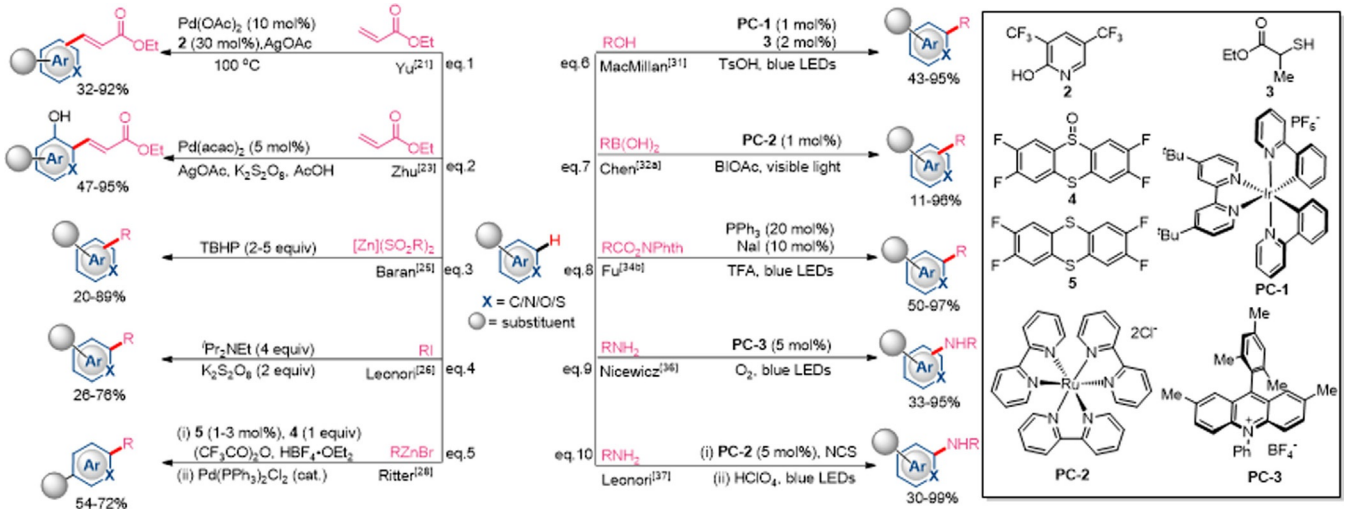

Figure 2. Key examples of recent aryl/heteroaryl C(sp^2)–H chemistries that have been successfully used for LSF of NPs or other complex bioactive compounds; acac = acetylacetone, TBHP = *tert*-butyl hydroperoxide, BIOAC = acetoxyl benziodoxole, TFA = trifluoroacetic acid, NCS = *N*-chlorosuccinimide, TsOH = *p*-toluenesulfonic acid, LED = light-emitting diode.

as strychnine, dasatinib, nefiracetam, boscalid, etofenprox, mizolastine, famoxadone, meclofenamic acid, and amiodarone.

The emergence of photoredox catalysis in the last decade has revolutionized organic chemistry.[29] Upon irradiation with low-energy visible light, photoredox catalysts are able to act as both single-electron oxidants and reductants to introduce reactive open-shell radicals with unconventional precursors. DiRocco et al. first reported the use of photoredox catalysis to conduct Minisci-type alkylation by using alkyl peroxides as radical precursors.[30] Later, through the combination of photoredox catalysis and a hydrogen-atom-transfer (HAT) thiol reagent (**3** in Figure 2), MacMillan and Jin reported the use of primary alcohols as radical precursors for the alkylation of heteroarenes [Figure 2, Eq. (6)].[31] Their method, however, requires the alcohol in a superstoichiometric amount (10 to 100 equiv). Chen et al. reported a photoredox-catalyzed Minisci-type C–H alkylation of heteroarenes with alkyl boronic acids as radical precursors [Figure 2, Eq. (7)];[32a] excellent FG tolerance (including terminal alkenes and alkynes) and LSF of complex NPs, such as strychnine, quinine, camptothecin, famciclovir, fenarimol, and fasudil, were demonstrated. This method was further improved by Molander et al. with the use of alkyltrifluoroborates as radical precursors.[32b] Impressively, all forms of alkyltrifluoroborates (1°, 2°, 3°) can be employed to alkylate heteroarenes with improved regioselectivity in the presence of an organocatalyst and a mild oxidant. Further appeal of this method was shown by its broad FG tolerance towards various carbonyl functionalities, free amides, and alcohols. Phthalimido esters, also known as redox-active esters (RAE), of carboxylic acids undergo facile radical decarboxylation under transition-metal-catalyzed redox conditions.[33] They are robust precursors for photoinduced Minisci-type alkylation without the requirement of external oxidants.[34,35] The first use of RAE in Minisci-type photoredox reactions was reported by Fu et al. in 2017,[34a] and more recently they developed a mild protocol for the alkylation of heteroarenes by using a novel electron-donor–acceptor (EDA) catalytic system employing only triphenylphosphine and sodium iodide under blue LED irradiation [Figure 2, Eq. (8)].[34b] By synergistically merging this redox catalytic system with a chiral Brønsted acid catalyst, asymmetric α-aminoalkylation of N-heteroarenes could be achieved with excellent enantioselectivity. A one-pot photoredox Minisci reaction, by directly employing carboxylic acids to generate RAE in situ, was recently demonstrated by Sherwood et al.[35]

In addition to carbon-centered radicals, the use of nitrogen radicals for aryl/heteroaryl C(sp^2)–H functionalization is also desirable due to the prevalence of amines in drugs and NPs.[1] In 2017, Nicewicz et al. reported an organic photoredox strategy for direct aryl C–H amination by using aminium radicals generated from primary alkyl amines [Figure 2, Eq. (9)].[36] This method holds great appeal for LSF, owing to 1) the direct use of primary alkyl amines as substrates; 2) the use of an organophotocatalyst (**PC-3** in Figure 2) with O_2 as the terminal oxidant, rendering the entire reaction conditions very mild; and 3) the broad scope of both simple and complex arene substrates with various primary amines. In another direct aryl C–H amination recently reported by Leonori et al. [Figure 2, Eq. (10)],[37] an N-chloroammonium intermediate was first generated in situ from the corresponding amine (1°, 2°), followed by single-electron reduction with a light-activated photocatalyst to deliver a highly reactive aminium radical, which underwent subsequent addition to arenes. This method displayed the immensely broad substrate scope of different arenes with structurally diverse secondary and primary amines, as well as FG tolerance of free alcohols, azides, terminal olefins, halogen, boron, and silicon. It was successfully utilized for LSF of drug molecules (e.g., ramipril, fenoprofen, dichlorprop, donepezil, dextromethorphan) and other bioactive compounds, such as peptides.

Potential Applications of LSF for In Situ Profiling of NPs

Notwithstanding the great strides that have been made in LSF of NPs and related bioactive compounds,[17a,b] its wide applications for in situ proteome profiling have not come to fruition thus far.[3,4,17c] One rare example of LSF in the generation of an ABP was reported by Romo et al., who identified potential protein targets of eupalmerin acetate (an NP with anticancer properties) by tagging the compound with a terminal alkyne linker through rhodium-catalyzed C–H amination or aziridination.[38] This method is, however, not suitable for late-stage aryl/heteroaryl C(sp^2)–H functionalization and incompatible with the use of diazirine-containing minimalist linkers (therefore, it is not possible for A*f*BP generation).

To take full advantage of LSF of aryl/heteroaryl C(sp^2)–H bonds, we envisage the following types of LSF chemistries could be immediately used for the installation of next-generation minimalist linkers (Figure 1 D), and to generate both ABPs and A*f*BPs from NPs and related bioactive compounds in a single-step operation (Figure 3). These methods are selected on the basis of operational ease; chemoselectivity; FG tolerance towards both the NP and the linker; and, finally, easy access of linker chemistry. Regioselectivity, on the other hand, is not a critical factor here because it is often advantageous to have diverse chemical probes with different tagging sites in a NP to investigate different target-binding modes. For next-gen-

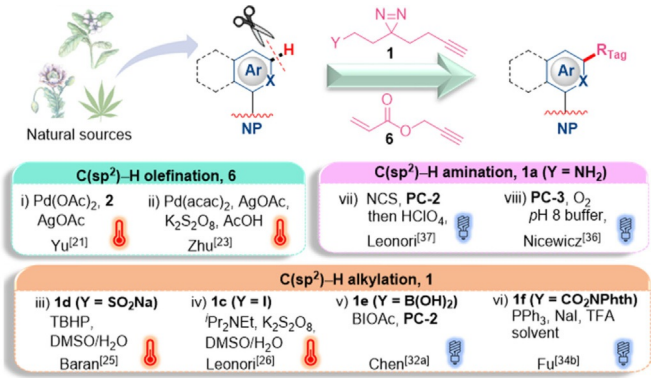

Figure 3. A) Proposed late-stage C(sp^2)–H functionalization of arenes in NPs with next-generation minimalist linkers. B) Various C(sp^2)–H functionalization chemistries compatible with minimalist NP tagging. New minimalist linkers (**1 d**–**f**) may be synthesized from existing linkers (**1 a**–**c**).

eration ABPs, the terminal alkyne-containing acrylate (**6** in Figure 3A) could be directly used with Yu's DG-free approach for LSF of various arenes (Figure 3B; condition i). For cases in which a NP contains a phenol, the same linker could be used under Zhu's conditions to afford exclusive *ortho*-olefination (Figure 3B; condition ii). By functionalizing NPs with an electrophilic trap, the resulting ABPs could be used to profile potential protein targets with intrinsic nucleophilic residues near their drug-binding sites (Figure 1B, top).

For next-generation A*f*BPs with diazirine-containing linkers (**1** in Figure 3A), the issue of premature photoactivation of diazirine in a photoredox LSF can be avoided by using photocatalysts with triplet energies lower than 60 kcal mol^{-1}.[39] Of the various methods chosen (Figure 3B; conditions iii–viii), Baran's zinc/sodium sulfinates **1d** stand out due to their impressive range of applications in LSF of bioactive molecules. Many of these sulfinates are bench-stable and LSF can be conducted in the open air. Terminal alkyne- and diazirine-containing sulfinates may be accessed from the iodide linker (**1c**, Y = I) under mild conditions (Figure 3B; condition iii).[40a] Similar tagging with **1c** by using Leonori's method (Figure 3B; condition iv) should be applicable to a variety of NPs as well. The acid linker (**1b**, Y = CO_2H) may be first converted into boronic acid **1e**,[40b] followed by NP tagging with Chen's method (Figure 3B; condition v). Alternatively, RAE **1f** could be readily obtained from **1b** by simple acylation,[33b] and used with Fu's method (Figure 3B; condition vi). Finally, C(sp^2)–H photocatalytic aminations with the amine linker (**1a**, Y = NH_2), under either acidic (Figure 3B; condition vii) or neutral pH (condition viii), with Leonori or Nicewicz's methods, respectively, would further expand our toolbox for late-stage C(sp^2)–H tagging of NPs and related bioactive compounds.

Summary and Outlook

Breakthroughs in organic chemistry have always been the major driving force in drug discovery and chemical biology. Traditional synthetic methodologies developed in the last 50 years still impose great limits on drugs that can be designed and made experimentally. The emergence of C–H activation chemistries capable of LSF of complex druglike molecules are now used widely by pharmaceutical companies. In situ drug profiling, a chemical biology tool developed ten years ago, with the aim of addressing off-target issues of drugs, on the other hand, has thus far mostly used tagged probes synthesized by traditional multistep organic transformations. LSF to arm NPs and related bioactive compounds, in a single-step operation, with next-generation minimalist linkers will provide chemical biologists with new toolkits to access probes modified at sites that were previously inaccessible. The fact that NPs and druglike molecules often contain aromatics, amines, and N-heterocycles, as well as unprotected polar groups, enables aryl/heteroaryl C(sp^2)–H functionalization to avoid tagging functionalities crucial for target binding. We are mindful, however, some LSF chemistries proposed herein remain limited in their substrate scope, FG tolerance, and selectivity. Both reaction outcome and selectivity are context dependent. The purpose of this Concept, nonetheless, is to encourage more experts in chemical biology to start embracing LSF in their endeavors to solve other equally important biological problems.

Acknowledgements

Funding was provided by the Ministry of Education (MOE; R-143-000-694-114, MOE2017-T2-2-081), the GSK-EDB Trust Fund (R-143-000-88-592), and the Synthetic Biology Research & Development Programme (SBP) of the National Research Foundation (SBP-P4 and SBP-P8) of Singapore.

Conflict of interest

The authors declare no conflict of interest.

Keywords: drug discovery · in situ proteome profiling · late-stage functionalization · natural products · proteomics

[1] K. C. Nicolaou, T. Montagnon, *Molecules That Changed the World*, Wiley-VCH, Weinheim, **2008**.
[2] S. Ziegler, V. Pries, C. Hedberg, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 2744–2792; *Angew. Chem.* **2013**, *125*, 2808–2859.
[3] M. H. Wright, S. A. Sieber, *Nat. Prod. Rep.* **2016**, *33*, 681–708.
[4] S. Pan, H. Zhang, C. Wang, S. C. L. Yao, S. Q. Yao, *Nat. Prod. Rep.* **2016**, *33*, 612–620.
[5] C. G. Parker, M. R. Pratt, *Cell* **2020**, *180*, 605–632.
[6] L. Dai, N. Prabhu, L. Y. Yu, S. Bacanu, A. D. Ramos, P. Nordlund, *Annu. Rev. Biochem.* **2019**, *88*, 383–408.
[7] A. Mateus, N. Kurzawa, I. Becher, S. Sridharan, D. Helm, F. Stein, A. Typas, M. M. Savitski, *Mol. Syst. Biol.* **2020**, *16*, e9232.
[8] Y. Su, J. Ge, B. Zhu, Y.-G. Zheng, Q. Zhu, S. Q. Yao, *Curr. Opin. Chem. Biol.* **2013**, *17*, 768–775.
[9] D. Kidd, Y. Liu, B. F. Cravatt, *Biochemistry* **2001**, *40*, 4005–4015.
[10] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075.
[11] B. F. Cravatt, A. T. Wright, J. W. Kozarich, *Ann. Rev. Biochem.* **2008**, *77*, 383–414.
[12] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.
[13] A. E. Speers, G. C. Adam, B. F. Cravatt, *J. Am. Chem. Soc.* **2003**, *125*, 4686–4687.
[14] a) S. A. Sieber, S. Niessen, H. S. Hoover, B. F. Cravatt, *Nat. Chem. Biol.* **2006**, *2*, 274–281; b) I. Staub, S. A. Sieber, *J. Am. Chem. Soc.* **2008**, *130*, 13400–13409; c) P.-Y. Yang, K. Liu, M. H. Ngai, M. J. Lear, M. R. Wenk, S. Q. Yao, *J. Am. Chem. Soc.* **2010**, *132*, 656–666.
[15] a) A. Saghatelian, N. Jessani, A. Joseph, M. Humphrey, B. F. Cravatt, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 10000–10005; b) E. W. Chan, S. Chattopadhaya, R. C. Panicker, X. Huang, S. Q. Yao, *J. Am. Chem. Soc.* **2004**, *126*, 14435–14446; c) J. Eirich, R. Orth, S. A. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 12144–12153; d) H. Shi, X. Cheng, S. K. Sze, S. Q. Yao, *Chem. Commun.* **2011**, *47*, 11306–11308; e) H. Shi, C. Zhang, G. Y. J. Chen, S. Q. Yao, *J. Am. Chem. Soc.* **2012**, *134*, 3001–3014.
[16] Z. Li, P. Hao, L. Li, C. Y. J. Tan, X. Cheng, G. Y. J. Chen, S. K. Sze, H.-M. Shen, S. Q. Yao, *Angew. Chem. Int. Ed.* **2013**, *52*, 8551–8556; *Angew. Chem.* **2013**, *125*, 8713–8718.
[17] a) M. Moir, J. J. Danon, T. A. Reekie, M. Kassiou, *Exp. Opin. Drug Discovery* **2019**, *14*, 1137–1149; b) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576; c) B. Hong, T. Luo, X. Lei, *ACS Cent. Sci.* **2020**, *6*, 622–635.
[18] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.

[19] D. T. Cohen, C. Zhang, C. M. Fadzen, A. J. Mijalis, L. Hie, K. D. Johnson, Z. Shriver, O. Plante, S. J. Miller, S. L. Buchwald, B. L. Pentelute, *Nat. Chem.* **2019**, *11*, 78 – 85.
[20] T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900 – 2936.
[21] P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung, J.-Q. Yu, *Nature* **2017**, *551*, 489 – 493.
[22] Q. Shao, K. Wu, Z. Zhuang, S. Qian, J.-Q. Yu, *Acc. Chem. Res.* **2020**, *53*, 833 – 851.
[23] Y. Dou, Kenry, J. Liu, J. Jiang, Q. Zhu, *Chem. Eur. J.* **2019**, *25*, 6896 – 6901.
[24] F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron* **1971**, *27*, 3575 – 3579.
[25] a) J. M. Smith, J. A. Dixon, J. N. deGruyter, P. S. Baran, *J. Med. Chem.* **2019**, *62*, 2256 – 2264; b) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95 – 99; c) Q. Zhou, J. Gui, C.-M. Pan, E. Albone, X. Cheng, E. M. Suh, L. Grasso, Y. Ishihara, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12994 – 12997.
[26] T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021 – 1026.
[27] R. S. J. Proctor, R. J. Phipps, *Angew. Chem. Int. Ed.* **2019**, *58*, 13666 – 13699; *Angew. Chem.* **2019**, *131*, 13802 – 13837.
[28] F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223 – 228.
[29] a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075 – 10166; b) C.-S. Wang, P. H. Dixneuf, J.-F. Soulé, *Chem. Rev.* **2018**, *118*, 7532 – 7585.
[30] 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.
[31] J. Jin, D. W. C. MacMillan, *Nature* **2015**, *525*, 87 – 90.
[32] a) G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu, G. Chen, *Chem. Sci.* **2016**, *7*, 6407 – 6412; b) J. K. Matsui, D. N. Primer, G. A. Molander, *Chem. Sci.* **2017**, *8*, 3512 – 3522.
[33] a) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213 – 218; b) C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355.
[34] a) W.-M. Cheng, R. Shang, Y. Fu, *ACS Catal.* **2017**, *7*, 907 – 911; b) M.-C. Fu, R. Shang, B. Zhao, B. Wang, Y. Fu, *Science* **2019**, *363*, 1429 – 1434.
[35] T. C. Sherwood, N. Li, A. N. Yazdani, T. G. M. Dhar, *J. Org. Chem.* **2018**, *83*, 3000 – 3012.
[36] K. A. Margrey, A. Levens, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15644 – 15648; *Angew. Chem.* **2017**, *129*, 15850 – 15854.
[37] A. Ruffoni, F. Juliá, T. D. Svejstrup, A. J. McMillan, J. J. Douglas, D. Leonori, *Nat. Chem.* **2019**, *11*, 426 – 433.
[38] J. Li, J. S. Cisar, C.-Y. Zhou, B. Vera, H. Williams, A. D. Rodríguez, B. F. Cravatt, D. Romo, *Nat. Chem.* **2013**, *5*, 510 – 517.
[39] J. B. Geri, J. V. Oakley, T. Reyes-Robles, T. Wang, S. J. McCarver, C. H. White, F. P. Rodriguez-Rivera, D. L. Parker, E. C. Hett, O. O. Fadeyi, R. C. Oslund, D. W. C. MacMillan, *Science* **2020**, *367*, 1091 – 1097.
[40] a) C. Tran, B. Flamme, A. Chagnes, M. Haddad, P. Phansavath, V. Ratovelomanana-Vidal, *Synlett* **2018**, *29*, 1622 – 1626; b) D. Wei, T.-M. Liu, B. Zhou, B. Han, *Org. Lett.* **2020**, *22*, 234 – 238.

Manuscript received: September 28, 2020
Revised manuscript received: November 4, 2020
Accepted manuscript online: November 6, 2020
Version of record online: December 22, 2020