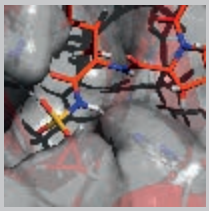
doi:10.2533/chimia.2022.258 Chimia 76 (2022) 258–260



Medicinal Chemistry and Chemical Biology Highlights

Division of Medicinal Chemistry and Chemical Biology

A Division of the Swiss Chemical Society

Late-Stage Functionalization and its Impact on Modern Drug Discovery

David F. Nippa[ab], Remo Hohler[b], Antonia F. Stepan[b], Uwe Grether[b], David B. Konrad*[a], and Rainer E. Martin*[b]

*Correspondence: Dr. R. E. Martin[b], E-mail: rainer_e.martin@roche.com; Dr. D. B. Konrad[a], E-mail: david.konrad@cup.lmu.de

[a]Department of Pharmacy, Ludwig-Maximilians-Universität München, 81377 Munich, Germany; [b]Medicinal Chemistry, Roche Pharma Research and Early Development (pRED), Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4070 Basel, Switzerland

Keywords: Catalysis · Diversification · Late-stage functionalization (LSF) · Medicinal chemistry· Methodology · Synthesis

Synthesis is key for accessing the vast, undiscovered chemical space and therefore at the heart of any drug discovery project. However, due to the structural novelty and complexity of drug molecules and their analogs, synthesis remains, in many cases, the rate-limiting step in building structure-activity relationships (SAR).[1] Rapid SAR exploration is an essential element for improving pharmacological activity and physicochemical properties of lead structures. Making synthetic strategies more efficient is paramount to the overall success of almost all drug discovery processes and ultimately for bringing novel drugs to patients. In that regard, the late-stage functionalization (LSF) of complex molecules, in which the C–H bond serves as a starting point for diversification, has emerged as a powerful and step-economical approach to rapidly explore closely related chemical space, and hence it is more and more routinely applied in drug discovery programs. Two different concepts can be pursued with LSF: on the one hand, the synthesis of a specific, single product and, on the other hand, a diversity-oriented approach to generate as many products as possible. Both approaches have been applied successfully in medicinal chemistry.[2] In the last two decades, the field of C–H bond functionalization has grown tremendously. Various catalytic systems are available that offer both directed and non-directed as well as chemo- and site-selective access to modified analogs. High functional group tolerance is critically important for the broad application of LSF methods (Fig. 1).[3–6]

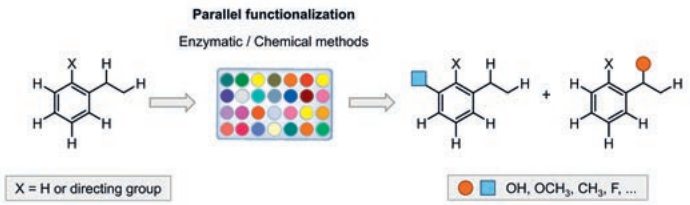


Fig. 1. Directed and/or non-directed late-stage diversification methods can accelerate access to new drug molecules considerably.

Over the past decade, the number of publications in the field has witnessed a significant increase in nearly all types of late-stage transformations. The results from a comprehensive literature search conducted in Scopus, Web of Science and SciFinder are depicted in Fig. 2.[7] The analysis of the literature search revealed that the LSF toolbox of today encompasses a large number of chemical and enzymatic methods such as fluorination,[8] amination,[9] hydroxylation[10] and methylation.[11] Over the last decade, tremendous progress towards providing reaction conditions for the functionalization of almost any sp^2 or sp^3 C–H bond without the need of installing a synthetic handle was made. In the following, we will provide an overview of LSF reactions and highlight their application to drug discovery projects using representative examples.

The number of publications (31) covering fluorination methodologies in the literature and their significant high average citation number (60) reflects the importance of C–F bond formations for drug discovery (Fig. 2). Late-stage fluorination can contribute to mitigating the metabolism of weak C–H bonds and to increase protein–ligand interactions. The Britton group developed conditions that allow the selective fluorination of pyridylic C–H bonds in the presence of benzylic moieties. This method was successfully applied to aldosterone synthase inhibitor **1**.[8] Furthermore, the same group has demonstrated that ^{18}F, which is commonly used in positron emission tomography (PET) ligands, can be introduced in a site-selective fashion at the leucine methine position in fully unprotected peptides.[12]

Amines find ubiquitous applications in medicinal chemistry, for example, as a means to optimize the interaction with the target of interest or to increase the solubility of drugs. They can also function as synthetic handles for further modification and serve as anchors for conjugation chemistry (*e.g.,* chemical biology tools, antibodies). With such a wide application scope, it is not surprising that, as of 2021, late-stage amination methodologies represent the second-largest reaction type subclass in LSF. Utilizing their newly developed conditions, Weis *et al.* demonstrated the advantage of late-stage amination in the synthesis of the Tranilast biotin conjugate **2**, which can be used as a probe in chemical biology studies.[9]

Non-covalent interactions between aromatic systems and proteins frequently increase potencies in pharmaceutically active molecules. While cross-coupling reactions are the major synthetic toolbox to introduce aryl systems, there is an increasing demand for a more cost- and step-effective synthesis, which reflects the large number of late-stage arylation methodologies published to date. Among those, Simonetti *et al.* presented an approach that allows the arylation of several known drugs, including Sulfaphenazole (**3**).[13]

A common phenomenon observed in medicinal chemistry is the magic methyl effect.[14] It describes the favorable modulation of pharmacological properties (*e.g.,* potency, metabolic stability, reduced CYP inhibition) solely achieved through the incorporation of a methyl group into a lead structure. Thus, the identification of

Can you show us your Medicinal Chemistry and Chemical Biology Highlight?
Please contact: Dr. Fides Benfatti, E-mail: fides.benfatti@syngenta.com, Syngenta Crop Protection, WST-820-2-15 Schaffhauserstrasse, CH-4332 Stein

effective late-stage methylation protocols has received increased attention within the LSF community. One of these methodology papers describes the cobalt-catalyzed C–H methylation, which was applied to Celecoxib (**4**) and other small molecule drugs.[11]

Modification of a molecule through oxidation can have a similar impact. In addition to improving solubility, late-stage oxidations can enable the identification, characterization, and assessment of potential metabolites at an early stage of drug design. In cases where highly regio- and stereoselective transformations are required, late-stage enzymatic oxidations have proven to be a powerful tool, often superior to chemical methods. A successful application is the biocatalyzed synthesis of phosphodiesterase inhibitor **5**. The incorporation of the hydroxyl group resulted in superior properties relative to the parent molecule, and, due to its favorable profile in rat and dog toxicology studies, compound **5** was selected as a potential clinical candidate.[10]

α-Ketones can function as convenient building blocks for drug discovery projects, as recently shown by Huan *et al.* The authors reported an asymmetric benzylic acylation enabling the synthesis of α-aryl ketones from carboxylic acids. Among other therapeutically relevant complex compounds, the authors also successfully achieved the functionalization of Flurbiprofen (**8**) as shown in Fig 2.[17]

Although we anticipate that LSF will soon become a routinely applied technology for the efficient synthesis of bioactive molecules, there are still considerable challenges to overcome. The plethora of drug modalities – ranging from small molecules to proteolysis-targeting chimeras (PROTACs), peptides, nucleic acid-based drugs, antibody drug conjugates and antibodies – offer great structural diversity and often contain very similar stereoelectronic C–H bonds. Therefore, a detailed understanding of the accessibil-

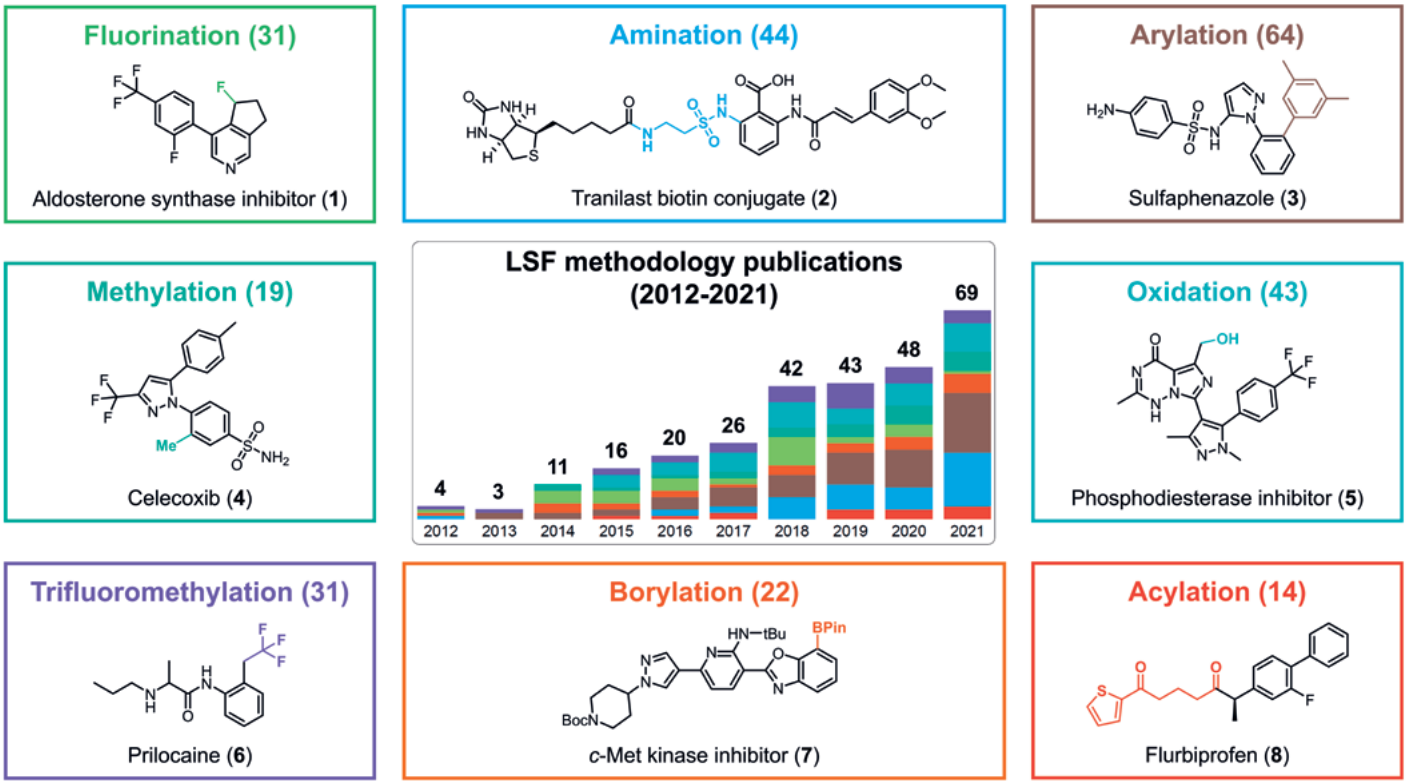


Fig. 2. Increase in publications of the most common LSF methodologies from 2012 to 2021 (center). Selected applications of LSF fluorination, amination, arylation, methylation, oxidation, trifluoromethylation, borylation and acylation found in literature. The number in brackets next to the methodology name states the publication count as of 2021.[7]

Trifluoromethylation enables the access to drugs with improved metabolic stability, increased permeability or potency. The MacMillan group showcased this *via* the photocatalytic trifluoromethylation of Prilocaine (**6**) and a small selection of other complex molecules.[15]

Although boron itself plays only a minor role in pharmaceuticals, the regioselective introduction of boron as a synthetic handle into advanced drug-like molecules offers an important strategy for late-stage diversification. The synthetic possibilities of post-borylation modification are very broad and provide a powerful approach to explore SARs through the incorporation of different functional groups. The significance of applying late-stage borylation chemistry is highlighted through the high number of citations that those publications received (average of 46 citations). One of many articles originating from the Hartwig lab demonstrated the efficient borylation of *c*-Met kinase inhibitor **7**.[16]

ity of a particular C–H bond for a given type of reaction is crucial. Moreover, improved tolerance towards common functional groups in bioactive molecules (*e.g.*, polar groups, basic groups and heterocycles) will be central for the broader utilization of LSF methods. This includes the development of milder reaction conditions, *e.g.*, the avoidance of high reaction temperatures, strongly acidic conditions and powerful oxidants, as these could cause undesirable side reactions.[2,5] The recent renaissance of photoredox, radical, and electrochemical reactions will complement the state-of-the-art research with novel C–H activation methods.[3,4] In addition, biocatalytic transformations used by nature to selectively modify polyfunctional compounds, offer great potential to address these challenges.[18] In the context of diversity-oriented synthesis, the discovery of novel reactions for the installation of transient handles such as boron or phosphorus containing groups will further complement the arsenal of LSF techniques.[6,19]

Low synthetic yields and technically demanding procedures are another obstacle often obtained with LSF transformation and have limited the application in process chemistry and scale-up campaigns. To address this objective, catalytic processes need to be further optimized, including, *e.g.,* the reduction of catalyst loadings and the increase of turnover rates, but also making these systems compatible with water and substituting toxic transition metal complexes in order to achieve more economical and 'greener' reactions.[20,21] The use of flow chemistry could contribute to this endeavor since it is ideally suited, *e.g.,* for scaling-up photo- and electrochemical transformations.[2]

LSF will also benefit from recent advances in high-throughput experimentation (HTE) and lab automation methods to rapidly and more efficiently search for optimal reaction conditions while drastically minimizing material consumption.[2,3] New technologies that facilitate the purification and identification of reaction products as well as the determination of pharmacological activity data will further increase the impact of the field. In addition, machine learning and artificial intelligence will facilitate the generation of tools for predicting reactivity and selectivity of individual C–H bond manipulations in a prospective manner thereby enabling the resource-economical and eco-friendly synthesis of a desired target molecule.[2]

Due to the collective efforts of many laboratories and partnerships between industry and academia, LSF is evolving at a rapid pace and will become increasingly important for designing, synthesizing and optimizing novel organic molecules and drugs in the future.

Acknowledgements

DBK acknowledges funding from the Fonds der Chemischen Industrie through a Liebig Fellowship and Roche Basel for funding the PhD position of DFN.

Received: January 31, 2022

[1] R. Jana, H. M. Begam, E. Dinda, *Chem. Commun*. **2021**, *57*, 10842, https://doi.org/10.1039/D1CC04083A.
[2] L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Rev. Chem*. **2021**, *5*, 522, https://doi.org/10.1038/s41570-021-00300-6.
[3] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev*. **2016**, *45*, 546, https://doi.org/10.1039/C5CS00628G.
[4] M. Moir, J. J. Danon, T. A. Reekie, M. Kassiou, *Expert Opin. Drug Discov*. **2019**, *14*, 1, https://doi.org/10.1080/17460441.2019.1653850.
[5] J. Börgel, T. Ritter, *Chem.* **2020**, *6*, 1877, https://doi.org/10.1016/j.chempr.2020.07.007.
[6] K. E. Kim, A. N. Kim, C. J. McCormick, B. M. Stoltz, *J. Am. Chem. Soc*. **2021**, *143*, 16890, https://doi.org/10.1021/jacs.1c08920.
[7] The literature analysis is based on the eight most impactful LSF methodologies for Medicinal Chemistry applications covering the time span from 2012-2021. Papers were found by the search algorithm if their title contained the name of the methodology (*e.g.,* methylation). To identify LSF methods in particular, 'late-stage' together with 'functionalization' or 'diversification' or 'modification' or 'activation' needed to be included in the abstract.
[8] M. Meanwell, M. B. Nodwell, R. E. Martin, R. Britton, *Angew. Chem. Int. Ed*. **2016**, *55*, 13244, https://doi.org/10.1002/anie.201606323.
[9] E. Weis, M. J. Johansson, B. Martín-Matute, *Chem. Eur. J*. **2021**, *27*, 18188, https://doi.org/10.1002/chem.202103510.
[10] A. F. Stepan, T. P. Tran, C. J. Helal, M. S. Brown, C. Chang, R. E. O'Connor, M. De Vivo, S. D. Doran, E. L. Fisher, S. Jenkinson, D. Karanian, B. L. Kormos, R. Sharma, G. S. Walker, A. S. Wright, E. X. Yang, M. A. Brodney, T. T. Wager, P. R. Verhoest, R. S. Obach, *ACS Med. Chem. Lett*. **2018**, *9*, 68, https://doi.org/10.1021/acsmedchemlett.7b00343.
[11] S. D. Friis, M. J. Johansson, L. Ackermann, *Nat. Chem*. **2020**, *12*, 511, https://doi.org/10.1038/s41557-020-0475-7.
[12] Z. Yuan, M. B. Nodwell, H. Yang, N. Malik, H. Merkens, F. Bénard, R. E. Martin, P. Schaffer, R. Britton, *Angew. Chem. Int. Ed*. **2018**, *57*, 12733, https://doi.org/10.1002/anie.201806966.
[13] M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, *Nat. Chem*. **2018**, *10*, 724, https://doi.org/10.1038/s41557-018-0062-3.
[14] H. Schönherr, T. Cernak, *Angew. Chem. Int. Ed*. **2013**, *52*, 12256, https://doi.org/10.1002/anie.201303207.
[15] P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y.-H. Lam, E. C. Sherer, D. W. C. MacMillan, *Nat. Chem*. **2020**, *12*, 459, https://doi.org/10.1038/s41557-020-0436-1.
[16] M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc*. **2014**, *136*, 4287, https://doi.org/10.1021/ja412563e.
[17] L. Huan, X. Shu, W. Zu, D. Zhong, H. Huo, *Nat. Commun*. **2021**, *12*, 3536, https://doi.org/10.1038/s41467-021-23887-2.
[18] E. Romero, B. S. Jones, B. N. Hogg, A. R. Casamajo, M. A. Hayes, S. L. Flitsch, N. J. Turner, C. Schnepel, *Angew. Chem. Int. Ed*. **2021**, *60*, 16824, https://doi.org/10.1002/anie.202014931.
[19] J. D. Lasso, D. J. Castillo-Pazos, C.-J. Li, *Chem. Soc. Rev*. **2021**, *50*, 10955, https://doi.org/10.1039/D1CS00380A.
[20] W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed*. **2018**, *57*, 14700, https://doi.org/10.1002/anie.201806250.
[21] J. Wencel-Delord, F. Glorius, *Nat. Chem*. **2013**, *5*, 369, https://doi.org/10.1038/nchem.1607.