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Enantioselective C–H Functionalization Recent Advances and Applications in Drug Discovery – A Review

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Abstract ***C–H functionalization represents a significant paradigm shift in the strategic framework of modern organic synthesis. Traditionally, synthetic methodologies have relied on the selective transformation of pre-installed functional groups, requiring multiple steps for functional group interconversion and protection–deprotection sequences. In contrast, C–H functionalization enables the direct activation and transformation of otherwise inert C–H bonds, allowing for the site-selective introduction of new functional groups within complex molecular architectures, even in the presence of more traditionally reactive functional groups. This approach offers a more atom-economical and step-efficient route to molecular diversification, thereby streamlining synthetic pathways. Despite several decades of pioneering advances in academia, organic synthesis continues to represent a major bottleneck in pharmaceutical research and development. From an industrial perspective, challenges such as achieving high regioselectivity, chemoselectivity, and scalability in C–H activation reactions remain significant. Addressing these limitations would substantially expand the utility of C–H functionalization strategies and accelerate the discovery and development of next-generation therapeutic agents. Significant synthesis challenges arise from the fact that drug molecules typically contain amines and N-heterocycles, as well as unprotected polar groups. There is also a need for new reactions that enable non-traditional disconnection more C–H bond activation and late-stage functionalization, as well as stereoselectively substituted aliphatic hetero cyclic ring synthesis, C–X or C–C bond formation. We also emphasize that syntheses compatible with biomacromolecules will find increasing use, while new technologies such as machine-assisted approaches and artificial intelligence for synthesis planning have the potential to dramatically accelerate the drug-discovery process.***

Keywords: C-H Functionalization; Nature Product, Total Synthesis, Drug Development

I. INTRODUCTION

We have witnessed the striking advancement of C-H functionalization in organic synthesis over the past decade. The continuous development of new C-H functionalization methodologies allows us to achieve more efficient synthesis and modification of complex molecules (Allen et al., 2016). C-H functionalization has been increasingly used in the synthesis of both natural product and drug molecule. To construct the C-C or C-X bond, we need to transfer reactive functional groups to what we want in traditional methods. There is a potentially significant advantage to employing C-H functionalization over the conventional methods considering atom, redox and step economy. (Brooks et al., 2014) In addition, C-H functionalization is normally catalyzed by a transition metal, which has great potential in large-scale industrial production. (Liao et al., 2016)

Figure 1

Kaiqi Chen et. al (2018)

Applications of C-H Functionalization in Nature Product Total Synthesis

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We have selected a few representative examples of natural product total synthesis facilitated by C-H functionalization which have been published in recent years (within 5 years). We sincerely apologize that due to the limited space we could not include all excellent works in the field. These examples are classified by C-O, bond formation. (Fier et al., 2013)

Constructing C–O bond via C-H Functionalization

Constructing C–O bond through C-H functionalization has been used in total synthesis widely. In 2016, Baran group reported a nineteen-step total synthesis of (+)- phorobol In this approach, a C-H oxidation strategy was used to increase the oxidative state. The TMS- protected alcohol 1 was oxidized to compound 2 by TFDO (Cherney et al., 2014). This method activated inert methylene to a hydroxyl group, which demonstrated the atom economy and redox economy of C-H functionalization. In the same year, Baran group also reported that the carbonyl or hydroxyl groups on the non- activated methylene and methyne groups could be obtained in a moderate to good yield by electrochemical oxidation (McCallum et al., 2016). Respectively, silicon, free hydroxyl, amine, amide, lactone and other groups were tolerable during this process. (+)-2-oxo-yahazunone was efficiently prepared from 50 g of compound 4, which proved the utility of this methodology. (Collins et al., 2013).

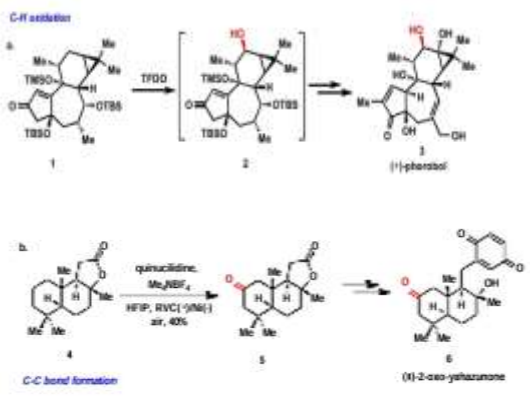

Figure 2
(Kaiqi Chen et aL., 2017).

II. THE VALUE–SYNTHESIS TRAJECTORY

The investment in the synthesis of an individual molecule or class of molecules in industry is generally linked to the relevance of the biological design hypothesis and also the stage of development of the drug-discovery project, as illustrated in Fig. 3. Significant synthetic resource is also justified for individual compounds if there is a strong and specific biological design hypothesis, such as a structure-based design utilizing a protein X-ray crystal structure. (Fox et al., 2016). In the initial stages of drug-discovery projects, small quantities (approximately 2–20 mg) of hundreds or thousands of molecules are designed, synthesized, characterized and tested in vitro. Value increases when biological activity is achieved and compounds are selected for in vivo evaluation, which typically requires ~0.1–1 g quantity. (Kilpin et al., 2015). At this stage, increased resources are applied to individual compound synthesis. Further evaluation of the biological profile and progression to safety assessment studies calls for additional investment in synthesis and the demands on chemistry change; methods need to be robust, scalable and safe. (Kutchukian et al., 2016). Figure 3 shows another value increase when a drug candidate is selected for clinical evaluation, which often involves its synthesis being scaled-up to ≥ 1 kg quantities. The compound may be handed over to process chemistry experts at this stage where extensive synthetic route optimization may be undertaken but ideally a scalable route will already have been defined through the joint efforts of discovery and development chemists. The process-chemistry development phase is critical but beyond the scope of this discussion. (Liu et al., 2015)

Significant synthetic challenges

Amines, nitrogen heterocycles and unprotected polar groups. From an industry perspective, the most common challenge for any new synthetic method is its level of tolerance to the polar functional groups and nitrogen heteroatoms found in biologically active molecules (Mercer et al., 2016). Drug molecules typically contain a number of often densely clustered, polar functional groups such as bases, weak protic acids, amides, amines, alcohols, hydrogen bond donors or acceptors, and nitrogen-containing

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heterocycles (Fig. 3a). These polar groups are specifically designed to confer high-affinity binding interactions with proteins and drug-like physicochemical properties. (Nadin et al., 2012). A key message is that the most commonly used reactions in early-stage drug-discovery projects will be those with the broadest scope in terms of compatibility of the reaction conditions towards substrates and products containing functional groups of the type shown in Fig. 3. Conversely, new published methods that are not exemplified with substrates bearing a range of these functionalities are less easily adopted without further experimental validation. (Siler et al., 2014)

Figure 3
(David C. Blakemore et aL., 2018)

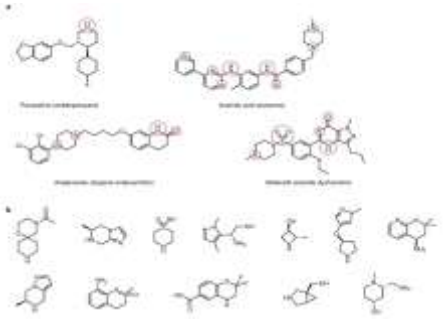

Figure 3
(David C. Blakemore et aL., 2018)

Syntheses involving nitrogen-containing compounds are well known to require protecting groups but this adds additional steps. As an example, the Suzuki–Miyaura coupling on tetra- hydropyrazolo[3,4-c]pyridines works well when both nitrogens are protected but fails when either is left unprotected (Fig. 4a)1Palladium-mediated aryl C–N bond-forming reactions, also known as Buchwald–Hartwig cross-couplings, are widely used. However, polar five-membered ring amino-heterocycles can be challenging substrates. (Yamada et al., 2010) For example, 1,3-oxazole-2-amines have proven difficult and the coupling with 2,4-chloropyridine proceeds in less than 3% yield (Fig. 4b)14. A long-standing solution to this problem has been to first couple methyl 2-amino-1,3-ox azole-5-carboxylate, hydrolyse and decarboxylate (Fig. 4). This strategy has been shown to work with a number of substrates, but it would be desirable to enable this transformation in a single step rather than taking a circuitous route through carboxyl ate intermediates and decarboxylation. (Zhang et al., 2016)

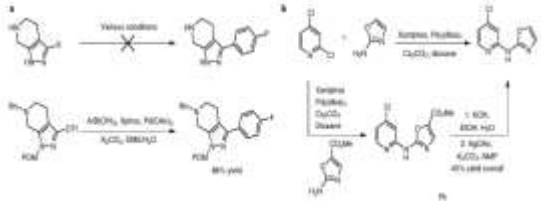

Figure 4

C–H bond activation and late-stage functionalization**.**

In terms of key strategic areas for industry, increasing interest has been paid to chemical transformations capable of directly modifying an existing bioactive molecule into a closely related analogue utilizing late-stage functionalization and C–H bond activation and encouraging progress has been made. (Siler et al., 2014). The advantage of this approach is that it is no longer necessary to initiate a new synthetic route for each target. However, the remaining challenge is to regiochemically functionalize a structurally complex polar molecule in a predict able way. Methodology that allows selective addition of for example methyl, fluoro or other small groups on each position of a (unprotected) lead molecule would be widely used in industry, although we recognize that this represents a significant scientific challenge for synthetic chemistry. (Xu et al., 2017). A related challenge is to discover new reactions that regioselectively activate each individual C–H bond in heterocycles within biologically active molecules. (Newhouse et al., 2011)

Natural products.

Natural products have long maintained a successful and important role in medicine. It has been estimated that nearly 50% of anticancer drugs introduced between the 1940s and 2014 are derived from, or inspired by, natural products or semi-synthetic derivatives, and there is renewed interest in natural products for targeting protein–protein interactions and for phenotypic screening strategies. The synthesis of natural products and their analogues to elucidate biological structure–activity relationships present major challenges for organic synthesis, including C–H bond activation and late-stage functionalization (Osberger et al., 2016).

A recent example of a synthetic transformation enabling more substantial structural modifications is the unexpectedly selective reaction of hexahydro-Diels–Alder benzynes with structurally complex natural products. Fully synthetic routes to natural products that deliver structures inaccessible through traditional semi-synthetic approaches are highly desirable, such as the convergent synthesis of macrolide antibiotics from simple chemical building blocks (Panish et al., 2016).

Moonshot synthesis.

Methodologies that enable selective single-atom exchange within organic molecules have the potential to transform strategies in medicinal chemistry. However, this emerging technology remains in its infancy and is highlighted here as an example of a transformative disconnection, without the expectation of immediate practical implementation (Romero et al., 2016). For instance, the replacement of a carbon atom with nitrogen within a heterocyclic framework represents a conceptual transformation of significant synthetic value. Such a hypothetical process might involve the use of a thiazolyl ‘nucleophile’ in combination with a thienyl ‘leaving group’, or alternatively proceed through ring opening followed by ring closure, conceptually related to the Dimroth rearrangement of amino-substituted triazoles in which endocyclic and exocyclic nitrogen atoms interchange positions (Shevlin et al., 2017).

The principal challenges include (i) achieving atom switching within a cyclic framework and (ii) enabling the exchange of a carbon atom for a heteroatom. Related challenges involve developing more versatile variants of established atom insertion or deletion reactions, such as the Baeyer–Villiger oxidation, Beckmann rearrangement, Arndt–Eistert homologation, and the Schmidt reaction, which converts ketones to the corresponding amides through nitrogen insertion, as well as the Curtius rearrangement of carboxylic acids to amines with the formal removal of one carbon atom (Wu et al., 2017).

III. NEW TECHNOLOGIES

Machine-assisted synthesis.

One of the principal reasons for the success of machine-assisted synthesis of biomacromolecules is the use of highly efficient and reproducible chemical transformations, including the formation of amide bonds, phosphodiester linkages, and anomeric centres in carbohydrates. In contrast, the synthesis of drug-like molecules generally requires a far broader spectrum of chemical transformations, each of which must operate efficiently and remain compatible within a unified synthetic platform (Campbell et al., 2014). Significant advances have been achieved by academic groups in automating specific chemical reactions or integrating them into continuous flow processes, as demonstrated in the work of Ley and Jamison. Nevertheless, considering the diversity of discrete chemical transformations involved, the development of fully automated synthesis systems without extensive optimization remains a considerable challenge.

One promising strategy to address this limitation is illustrated by the work of Burke, which emphasizes the use of the versatile Suzuki cross-coupling reaction to construct a wide range of molecular architectures from modular building blocks. Additional demonstrations involving small sets of compatible reactions would further validate this emerging and promising approach. In one such example, the distinct solvent–solubility characteristics of reagents and intermediates were exploited to establish simplified purification protocols, thereby minimizing the reliance on

extensive chromatographic separation (Flick et al., 2017).

Despite these advances, achieving rapid and efficient purification remains a major obstacle, highlighting the need for stronger collaboration between synthetic and analytical chemists. To facilitate compatibility with automated platforms, new synthetic methodologies should be developed and evaluated not only in conventional round-bottomed flasks but also within reaction vials and flow reactors, which are becoming increasingly prevalent in machine-assisted synthesis. Methods designed with automation in mind are more likely to be adopted within industrial settings. Achieving this goal will require closer collaboration between synthetic chemists, robotic scientists, and engineers. Furthermore, for these innovations to gain widespread application, the associated engineering solutions must become commercially accessible, either through equipment that integrates automated chemical methodologies or through services offered by emerging technology-focused companies (Meanwell et al., 2016).

Artificial intelligence for synthesis planning.

Reaction prediction is a major challenge for organic synthesis. There is a resurgence of interest based in part on the availability of enormous, publicly accessible databases containing chemical reactions and syntheses in a machine-readable format (Mercer et al., 2016). Current research is underway to devise algorithms that learn from published synthesis examples and hence aim to predict the outcome of new transformations.

This would be facilitated by ways to incentivize publishing of negative data; that is, reactions that do not work. Molecular descriptors based on physicochemical properties may be able to characterize reagents whilst neural networks that utilize known reaction mechanisms may assist the prediction of reaction outcomes. Recently a collection of over one-million chemical reactions has been gathered by applying text mining to published patent data. (Gensch et al., 2017)

This is being used to validate a computational fingerprint method to classify and then predict chemical reactions. In another recent study, a database of 3.5 million published reactions has been utilized to construct a machine-learning model for retrosynthesis and reaction prediction152.

Application of C-H Functionalization in Drug Molecule Synthesis

As a powerful strategy, C-H functionalization has been broadly employed in medicinal and process chemistry for drug development. Anacetrapib, a potent and selective CETP inhibitor, was synthesized successfully in process chemistry by Merck via Ru-catalyzed C-H Functionalization Fig. 5 (Durak et al., 2016). In this scalable synthesis, oxazoline was used as a directing group, which could be facilely transformed to the desired alcohol at latter stage. Using this strategy, anacetrapid was efficiently prepared in only 5 steps

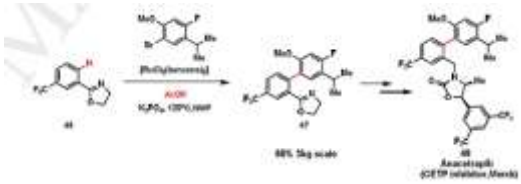

Figure 5: Scalable synthesis of anacetrapib via selective C-H Arylation.

CONCLUSION

C–H functionalization has proven to be an extremely powerful approach in organic synthesis. It offers remarkable atom, step, and operational economy, along with exceptional flexibility for late-stage structural modification of molecules. In several recent studies, C–H functionalization has also demonstrated its scalability in the multi-step synthesis of complex molecules, highlighting its growing importance in modern synthetic chemistry. Despite these advances, selective C–H functionalization remains a rapidly developing field, and many significant synthetic challenges still need to be addressed. Continued collaboration between academic and industrial chemists will be essential to overcome these challenges and to develop more robust and practical methodologies. Ultimately,

further progress in synthetic methods such as C–H functionalization will accelerate the synthesis of drug molecules and have a profound impact on drug discovery and human health.

AUTHOR'S CONTRIBUTION

The authors collaboratively prepared this review on enantioselective C–H functionalization and its applications in drug discovery. They contributed to the conceptualization of the topic, comprehensive literature survey, critical analysis of recent advances, and the writing and revision of the manuscript. Their combined efforts ensured the scientific rigor, coherence, and clarity of the review.

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