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In the past decade, multiple catalytic C–H bond functionalization has been successfully applied in natural product synthesis as a strategy to reduce the number of steps, increase overall yield and employ more easily available starting materials. This minireview presents selected examples making use of multiple C–H bond functionalization in conceptually different ways. First, linear syntheses are discussed, wherein multiple C–H functionalization is employed either from simple (hetero)cyclic cores, at a late stage, or to build polycyclic systems. Second, the use of multiple C–H functionalization as a strategic tool in convergent synthesis to access and couple complex fragments is discussed. Information on the scalability of the employed methods is provided when available. The presented cases indicate that multiple C–H functionalization strategies should play a great role to shape the future synthesis of functional complex molecules with improved sustainability.

1. Introduction

Transition-metal-catalyzed C–H bond activation and functionalization is an old research field that witnessed a spectacular expansion in the last two decades.^[1] A great number of methods have been recently developed for the functionalization of different types of C–H bonds, allowing the step-economical access to valuable building blocks for the synthesis of complex molecules, or the generation of compound libraries in a so-called late-stage approach.^[2] While the field continues to expand at a rapid pace, the chemoselectivity and scalability of the developed methods are being evaluated in the highly demanding context of natural product synthesis. Figure 1 shows that total synthesis has significantly expanded as a subtopic of C–H activation/functionalization in the past 20 years, and this topic has been already covered by a number of leading reviews.^[3]

Figure 1. Number of articles published in journals on the topic “C–H activation” or “C–H functionalization” and “total synthesis” in the last 40 years (source: SciFinder).

In this context, strategies incorporating multiple catalytic C–H functionalization reactions should be advantageous to streamline the synthesis of complex molecules. Indeed, they should enable the step-economical construction of key fragments by employing more readily available starting materials such as (cyclic) hydrocarbons, heterocycles and molecules from the chiral pool. Moreover, these strategies could avoid lengthy functional group interconversions and protection/deprotection steps. Finally, they could also provide more direct retrosynthetic disconnections in the context of convergent synthesis. However, in light of the plethora of recently developed C–H functionalization methods and a certain lack of hindsight on their applicability, synthetic chemists may still find

it difficult to consider to employ C–H functionalization instead of more established strategies when planning a new retrosynthetic analysis. This Minireview aims at contributing to change this perception by presenting, in a retrosynthetic format, selected recent total syntheses that incorporate multiple catalytic C–H functionalization in a linear or convergent pathway. In linear syntheses, multiple C–H functionalization of a cyclic core leads to the rapid increase of complexity from simple precursors. Alternatively, multiple C–H functionalization can be employed at a late stage to install key functional groups on an advanced intermediate. On the other hand, convergent syntheses can make use of multiple C–H functionalization to streamline the synthesis and/or the assembly of key fragments.

2. Linear Syntheses Featuring Sequential C–H Functionalization of Cyclic Systems

The synthesis of cyclic and polycyclic natural products often involves multiple functionalizations and functional group interconversions of simple carbo- or heterocyclic cores, which have a great impact on the overall number of steps and efficiency.

In this regard, using multiple C–H functionalization instead of more traditional methods can significantly improve the step count and overall yield. Examples in this section are classified as a function of the nature of the cyclic core undergoing C–H functionalization. In contrast, when multiple catalytic C–H functionalization is utilized on an advanced

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intermediate at the last stage of a synthesis, lengthy endgames can be avoided. Finally, multiple C–H functionalization can serve to rapidly construct complex polycyclic systems.

2.1. Sequential C–H functionalization of a benzene core

The starting point of the total synthesis of a hypothetical natural product scaffold **A** containing a benzene ring (Figure 2) is ideally a minimally functionalized monocyclic precursor **B** wherein a first functional group serves as directing or orienting group to selectively functionalize one or several other positions, which may themselves serve as new directing/orienting groups to reach other C–H bonds. The resulting sequential C–H functionalization sequence ultimately leads to the natural product along a linear pathway.

Figure 2. Syntheses involving the iterative C–H functionalization of a benzene core.

The enantioselective synthesis of (–)-incarviate A (**1**), reported in 2015 by Li, Lei and co-workers provides a perfect illustration of this concept (Scheme 1).^[4] Incarviate A is a hybrid natural product which revealed as a potent inhibitor of monoamine oxidase.^[5] The fused polycyclic system of **1** was thought to originate from polysubstituted indane **2**, which herein represents the C–H functionalization retron. The bromine atom, required for the late-stage introduction of the cyclopentene ring by Suzuki–Miyaura cross-coupling, was installed through sterically-controlled, *meta*-selective Hart-

Scheme 1. Synthesis of (–)-incarviate A by Li, Lei and co-workers. MOM = methoxymethyl.

wig-Smith-Miyaura C–H borylation^[6] and one-pot copper-mediated bromination^[7] from precursor **3** (3 g scale). The protected hydroxymethyl group in **3** was introduced from indane **4** through a modification of the carboxylic acid-directed, Pd^{II}-catalyzed C–H iodination method reported by J.-Q. Yu and co-workers,^[8] followed by Pd-catalyzed carbonylation and reduction (7 g scale). The cyclopentane ring in compound **4** was constructed by intramolecular Rh^I-catalyzed C–H insertion from diazo precursor **5**,^[9] hence showcasing another catalytic C–H functionalization step in addition to the multiple C–H functionalization at the benzene core. The two stereogenic centers in **4** were controlled through a mixed chiral auxiliary (R* = borneol)/chiral catalyst strategy, previously employed in total syntheses by Yu, Davies and Zakarian.^[10] Finally, the *n*-propyl chain in **5** was connected to the benzene ring by using again the directing group ability of the free carboxylic acid in phenylacetic acid **6**. Application of Yu's *ortho*-C–H alkylation protocol^[11] with *n*-propylboronic acid, catalyzed by Pd^{II} and a mono-protected amino acid (MPAA) ligand and using silver carbonate as stoichiometric oxidant, furnished the corresponding *ortho*-alkylated product in 30% yield, along with the di-*ortho*-alkylated product (10%) and recovered starting material (9%). Although the yield is modest for a first step, it employs inexpensive phenylacetic acid **6** and can be conducted on a gram scale. In this synthesis of incarviate A, the carboxylic acid in **6** is the directing group initiating the sequential C–H functionalization of the benzene core. Overall, (–)-incarviate A was obtained in only 14 steps, thereby illustrating the step-economy generated by multiple C–H functionalization.

The synthesis of K-252c (staurosporinone, **7**), disclosed by Gaunt and co-workers in 2016,^[12] provides another remark-

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able example of sequential C–H functionalization from a benzene core (Scheme 2). Staurosporinone belongs to a family of indolocarbazole alkaloids showing potent inhibition of protein kinase C.^[13] It comprises a fully substituted benzene core fused to two indolines and one γ -lactam ring. The Gaunt synthesis employs dibenzyl *p*-toluidine **11** as a simple and cheap starting material wherein the amino group is the directing/orienting group controlling the site-selectivity of the first C–H functionalization steps. During the synthesis of target **7**, the two carbazole rings were assembled by intramolecular C–H amination reactions that complement C–H functionalization of the benzene core. The first C–H amination involved a Cadogan-type nitrene insertion^[14] from nitro-substituted precursor **8**, which is the serial C–H functionalization retron for this synthesis. Then, the γ -lactam ring was constructed using an amine-directed Pd^{II}-catalyzed C–H carbonylation, adapted from the method reported by Orito and co-workers.^[15] Friedel–Crafts nitration and copper-catalyzed intramolecular C–H amination according to Chang^[16] further simplified intermediate **9** to the less substituted terphenyl precursor **10**. The two phenyl groups in **10** were installed from **11** through a sequence of *ortho* and *meta*-selective copper-catalyzed C–H arylations, directed by the amino group and based on previous methodological work from the Gaunt group. In the forward sense, the dibenzylamino group in **11** directed a copper(II)-catalyzed *ortho*-C–H arylation using diphenyliodonium triflate as the coupling partner,^[17] which occurred in good yield (76%), with high positional and mono selectivity on a 2.5 g scale. Then, switching the amine to an amide group allowed application of a *meta*-selective, copper-catalyzed arylation with the same diphenyliodonium reagent,^[18] which delivered compound **10** in 96% yield on a 4 g scale. This total synthesis displays an overall yield of 12.7% over 10 steps, features 4 C–H functionalization steps (including 3 copper-catalyzed ones)

Scheme 2. Synthesis of K-252c (staurosporinone) by Gaunt and co-workers. Ar = 2,6-Me₂C₆H₃.

on the benzene core and 2 additional ones to construct the (fused) carbazoles. This synthesis also showcases the complementarity of precious (Pd) and first-row (Cu) transition-metals to achieve challenging transformations.

On a similar note, Baidya and co-workers recently reported the formal synthesis of naturally occurring prenylated stilbenes by multiple C–H functionalization of a benzene core.^[19]

2.2. Sequential C–H functionalization of a saturated carbocyclic core

The total synthesis of piperarborenines by Gutekunst and Baran provides an prototypical example of multiple C–H functionalization from a saturated carbocyclic core, in this case a cyclobutane ring (Scheme 3).^[20] Piperarborenines are dimeric natural products exhibiting in vitro cytotoxicity against cancer cell lines.^[21] The synthesis of (±)-piperarborenine B (**12**) is based on the iterative, *cis*-diastereoselective C–H arylation of the cyclobutane core from acid-ester **16**, which was synthesized on a gram scale from methyl coumate by photochemical 4 π -electrocyclization and hydrogenation. The C–H functionalization retron **13** contains the 2-methylthioaniline directing group introduced by Daugulis.^[22] Such bidentate directing groups have proven particularly efficient for the functionalization of strong C(sp³)–H bonds, and for this reason they have been employed in a number of total syntheses.^[23] The palladium(II)-catalyzed C–H arylation of intermediate **14** with 3,4-dimethoxyiodobenzene provided a 46% yield on a gram scale. The reaction selectively occurred on the most sterically accessible, methylene position adjacent to the directing group and with exclusive *cis*-diastereoselectivity arising from strain minimization. The introduction of the trimethoxyphenyl group located *trans* to the dimethoxyphenyl group using the same method required precursor **15** wherein the directing group has the opposite configuration to

Scheme 3. Synthesis of (±)-piperarborenine B by Baran and co-worker. Ar = 2-SMeC₆H₄.

14. In the forward sense, after Pd-catalyzed C–H arylation of **15** with 3,4,5-trimethoxyiodobenzene (gram scale, 52 % yield), the selective epimerization at the amide directing group could be performed in the presence of the ester using LiOt-Bu in toluene. This judicious epimerization allowed introduction of the second aryl group with the appropriate relative configuration, and then completion of the total synthesis of the target molecule with the correct stereochemistry. This contributed to a short (7 steps) and efficient (7 % overall yield) synthesis of (±)-piperarborenine B.

2.3. Sequential C–H functionalization of a heterocyclic core

The sequential C–H functionalization of nitrogen heterocycles provides a step-economical entry into alkaloids. Unlike carbocycles, heterocycles benefit from strong electronic effects that may allow to differentiate the different C–H bonds without recourse to a directing group. A pioneering example was reported in 2008 by Gaunt and co-workers with the synthesis of (±)-rhazicine, which involved the sequential functionalization of a pyrrole core via C–H borylation and intramolecular Fujiwara–Moritani reaction.^[24] In the same year, Hoarau and co-workers reported the synthesis of the di(hetero)aryloxazole natural products balsoxin and texaline through the sequential C–H arylation of an oxazole core.^[25] Similarly, the total synthesis of the polyheterocyclic natural product dragmacidin D by Yamaguchi, Itami and co-workers involved two catalytic C–H functionalizations at one of the indole rings.^[26]

In 2015, two concurrent reports by the Itami–Yamaguchi/Davies and Gaunt groups disclosed the synthesis of dictyodendrins via sequential C–H functionalization of a pyrrole core, and these two examples were herein chosen for comparative purposes. Dictyodendrins are pyrrolocarbazole natural products of marine origin possessing telomerase inhibitory properties.^[27] The collaborative synthesis of dictyodendrins A (**17**) and F by the Davies and Itami–Yamaguchi groups involves the sequential C–H functionalization of the simple *N*-substituted pyrrole **21** (Scheme 4).^[28] Disconnections of dictyodendrin A at the carbazole ring by a formal 6 π -electrocyclization and a Suzuki–Miyaura coupling unveils the hidden symmetry in **17** and leads to C–H functionalization retron **18** bearing identical substituents at the C2 and C5 positions of the pyrrole ring. These were introduced from precursor **20** through a rhodium(II)-catalyzed double C–H insertion of the corresponding donor-acceptor aryldiazoacetate, and the bromine atom in **18** was introduced at the C4 position by one-pot electrophilic bromination. The mono-C–H insertion of diazo-derived carbenes on pyrroles was previously reported,^[29] but achieving a good yield and site-selectivity for the 2,5-dialkylated product **19** required significant experimentation. This was realized through a one-pot sequential dialkylation protocol and the use of the bulky paddlewheel rhodium complex Rh₂(S-TCPTAD)₄ developed by the Davies group (82 % yield for **19**).^[30] The *p*-methoxyphenyl group in compound **20** was then selectively introduced through application of a β -selective arylation method previously reported by the Itami–Yamaguchi group employing

Scheme 4. Synthesis of dictyodendrin A by Yamaguchi, Itami, Davies and co-workers.

a rhodium(I)-phosphite catalyst (gram scale, 52 % yield).^[31] Since the last three steps to access dictyodendrin A were already reported, the authors accomplished the formal synthesis of this molecule in 12 steps. They also synthesized dictyodendrin F from an intermediate in the sequence from **18** to **17**.

Shortly after, Gaunt and co-workers reported the total synthesis of another dictyodendrin congener, dictyodendrin B (**22**), also employing a multiple C–H functionalization strategy from a heterocyclic core (Scheme 5).^[32] However, in contrast to the above synthesis, they considered the indole nucleus embedded in the pyrrolocarbazole ring as the starting platform, taking advantage of its high reactivity and rich C–H functionalization chemistry.^[33] The C–H functionalization retron **23** was disconnected at the C5–N bond of the indole ring and the carbazole ring built by intramolecular nitrene insertion of an azide precursor, which was performed in continuous-flow to minimize the hazards associated with exothermic azide decomposition on scale. This process allowed production of one gram of product **23**, which can be converted to target **22** in 5 steps. The introduction of the C6 methoxy group was realized through a site-selective electrophilic bromination and copper-mediated methoxylation, retrosynthetically leading to intermediate **24**. Suzuki–Miyaura coupling at C4 and *N*-alkylation further simplified the structure. Then, the C7 aryl group was selectively introduced via iridium-catalyzed C–H borylation,^[6] exploiting the directing ability of the free NH group and the presence of the keto substituent blocking the C2 position,^[34] and one-pot Suzuki–Miyaura coupling, performed on multigram quantities. The corresponding precursor **25** was further disconnected at C2 and C3, taking advantage of the nucleophilicity of the indole ring at these positions. In the forward sense, the aryl group at

Scheme 5. Synthesis of dictyodendrin B by Gaunt and co-workers.

C3 was installed via copper-catalyzed C–H arylation with the appropriate diaryliodonium reagent,^[35] which was conducted on a 42 g scale in 68 % yield, and the keto group was installed at C2 via a catalytic Friedel–Crafts acylation, hence leading to commercial indole **26** bearing a single bromine substituent at C4.

This total synthesis of dictyodendrin B, executed in only 14 steps and scalable until its protected form **23**, illustrates the complementarity of classical C–H functionalization (e.g., electrophilic aromatic substitution and nitrene insertion) with more recent transition-metal-catalyzed methods for the multiple functionalization of simple (hetero)aromatic cores.

2.4. Late-stage functionalization of a (poly)cyclic framework

Non-catalyzed oxidative C–H functionalization has been recently established to mimic the oxidase phase in the synthesis of oxidized complex terpenes. In particular, Chen and Baran reported the synthesis of various eudesmane sesquiterpenes wherein a double C–H functionalization from a less oxidized sesquiterpene precursor, dihydrojunenol, serves as the oxidase phase.^[36] By analogy, late-stage transition-metal-catalyzed multiple C–H functionalization should represent a rapid entry into complex natural products from less complex natural precursors. This concept is nicely illustrated by the collaborative semi-synthesis of (+)-hongoquercin A (**27**), a fungal sesquiterpene with antibiotic properties,^[37] reported in 2013 by the Yu and Baran groups

Scheme 6. Semi-synthesis of (+)-hongoquercin A by Yu, Baran and co-workers.

(Scheme 6).^[38] Target **27** was thought to arise from a less functionalized sesquiterpene, (+)-chromazonarol (**29**), which was itself previously synthesized by the Baran group in 6 steps from the commercially available sesquiterpene (+)-sclareolide (**30**).^[39] The authors envisioned to employ the carboxylic acid in **27**, or a derivative thereof, as directing group to introduce the *ortho* methyl and hydroxy groups according to palladium(II)-catalyzed methodologies previously developed by the Yu group.^[40] Both the carboxylic acid **28a** and the more reactive perfluorophenylamide **28b** were actually considered as precursors. The C–H methylation was conducted first and the C–H oxidation second due to steric considerations. The C–H methylation of the weakly coordinating carboxylic acid **28a** with methyltrifluoroborate^[40a] required addition of a mono-protected amino acid ligand (Boc-phenylalanine)^[41] and furnished the desired monomethylation product in 45 % yield. Unfortunately, the O₂-mediated Pd-catalyzed C–H hydroxylation^[40b] of the resulting product was low yielding (ca. 15 %). Resorting to the more strongly coordinating amide **28b**, easily obtained from **28a**, provided a less direct, but more effective solution. The C–H methylation of **28b** occurred in 60 % yield without added ligand^[42] and the C–H hydroxylation was performed via Pd^{II}-catalyzed C–H acetoxylation^[43] (54 % yield) and ester hydrolysis. In turn, carboxylic acid **28a** was derived from phenol **29** via palladium(0)-catalyzed hydroxycarbonylation. Overall, (+)-hongoquercin A was obtained in 6 steps from (+)-chromazonarol and 12 steps from commercial (+)-sclareolide. Moreover, intermediates **28a,b** were employed as platforms for various Pd- and Rh-catalyzed directed C–H activation reactions, hence leading to a library of hongoquercin analogues and showcasing the potential of C–H activation for the late-stage functionalization of bioactive molecules.^[2]

2.5. Multiple C–H functionalization for the construction of polycyclic system

In addition to the previous cases, multiple catalytic C–H functionalization can be employed to build several rings, ideally in a single step, and access complex polycyclic systems. In this regard, palladium(0)-catalyzed double C–H functionalization employing dihalogenated precursors has proven a powerful approach (Figure 3).^[44] As an illustration, disconnection of the hypothetical pentacyclic framework **C** at the highlighted C–C bonds provides the simple tricyclic precursor **D** containing two C–H and two C–X bonds, hence offering improved atom and step economy compared to traditional cross-couplings, that one could have previously envisioned for such disconnections.

Figure 3. Construction of polycyclic systems by Pd⁰-catalyzed double C–H functionalization.

The synthesis of calothrixin B (**31**), an antimalarial and cytotoxic plant alkaloid,^[45] by Kumar and co-workers provides a simple illustration of this strategy (Scheme 7).^[46] The pentacyclic target **31** was traced back to the less oxidized C–H functionalization retron **32**, which was deconstructed by means of Pd⁰-catalyzed double C(sp²)–H arylation to give the dihalogenated tricyclic precursor **33**. Optimized conditions involving a combination of Pd(OAc)₂ with an unusual mixture of JohnPhos [JohnPhos = 2-(di-*tert*-butylphosphino)-biphenyl] and PCy₃ as the catalyst furnished the double C–H arylation product **32** in 88% yield. The order of C–H arylation events was presumably controlled by the oxidative addition steps, with the first C–H arylation occurring after the easier oxidative addition of the C–I bond to Pd⁰. Ultimately, intermediate **33** was synthesized from commercially available precursors **34–36** via Buchwald-Hartwig and reductive aminations, hence furnishing a six-step synthesis of calothrixin B.

Scheme 7. Synthesis of calothrixin B by Kumar and co-workers.

The synthesis of γ -lycorane (**37**), a degradation product of the pentacyclic *Amaryllidaceae* alkaloid lycorine,^[47] by our group provides another interesting example of double C–H functionalization to rapidly construct polycyclic systems (Scheme 8).^[48] Target **37** arose from precursor **38** via

Scheme 8. Synthesis of (±)- γ -lycorane by Baudoin and co-workers.

selective hydrogenation of the most strained benzene ring (D). Disconnecting two C–C bonds in **38** by means of Pd⁰-catalyzed double C–H arylation led to dihalogenated precursor **39**. In contrast to the previous target (Scheme 7), the construction of **38** through double C–H functionalization raised site-selectivity issues that were solved through a careful choice of the nature and position of halogen atoms on the reaction substrate. Indeed, the bromine atom on the B ring directed the first C–H arylation, which took place at the most reactive C(sp²)–H position on the D ring, and the second arylation occurred between the less reactive C–Cl bond and the activated C(sp³)–H position adjacent to the amide group. Positioning both halogen atoms on the D ring resulted in the formation of the wrong regioisomeric product due to the preferential C–H activation at the B ring in *ortho* position to the dioxolane ring. Finally, intermediate **39** was obtained in a single step from commercially available precursors **40–41**. Overall, racemic γ -lycorane was obtained in 47% yield over only 4 steps, thereby illustrating the power of the double C–H functionalization strategy to streamline access to polycyclic natural products.

The power of this ring-forming multiple C–H functionalization strategy was recently demonstrated in a more complex setting. It was indeed a key strategy in the divergent synthesis of the fused pentacyclic dithiodiketopiperazines (DTPs) (–)-epicoccin G (**42**) and (–)-rostratin A (**43**), bioactive secondary metabolites of fungal origin,^[49] which was reported by our group in 2019 (Scheme 9).^[50] These targets were obtained in 7 and 11 steps, respectively, from the less functionalized common intermediate **44**, which is here the C–H functionalization retron. In particular, the two alkenes in **44** were employed to access both *cis* and *trans* A–B/D–E ring junctions found in the natural products. The *trans*-fused system is particularly challenging to install and DTPs such as **43** had so far resisted total synthesis. Retron **44** was constructed from ditriflate **45** through Pd⁰-catalyzed double C(sp³)–H alkeny-

Scheme 9. Synthesis of (–)-epiccoccin G and (–)-rostratin A by The-smar and Baudoin.

lation, adapted from previous methodological work.^[51] After some experimentation required to suppress epimerization and achieve full conversions, the double C–H activation reaction was successfully performed on a decagram scale and in 93 % yield using the well-defined $\text{Pd}(\text{PCy}_3)_2$ catalyst, thus allowing production of sufficient amounts of common intermediate **44** for the completion of both total syntheses. In turn, the symmetrical dinitrile **45** was obtained from commercially

available L-alanine-*tert*-butyl ester **46** and cyclohexenone **47** through a retrosynthetic sequence including cyclocondensation, epoxide ring opening and enantioselective organocatalytic epoxidation. Overall, (–)-epiccoccin G and (–)-rostratin A were synthesized in 19.6 % over 14 steps and 12.7 % yield over 17 steps, respectively, and the synthesis of (–)-rostratin A was scaled up to yield over 500 mg of substance. The key double C–H functionalization had an impact in both reducing the number of steps and increasing the overall yield to access the common intermediate **44** leading to both targets.

3. Multiple C–H Functionalization in Convergent Syntheses

The previous part showcased multiple C–H functionalization in the context of linear total syntheses. In a complementary manner, such approaches can be employed in convergent synthesis, either to streamline the synthesis of fragments, and/or as key transform to couple these fragments.

3.1. Convergent syntheses wherein several fragments are constructed by C–H functionalization

Aeruginosins are dipeptide natural products isolated from various marine organisms that showed potent inhibition of serine proteases.^[52] In 2015, the synthesis of four aeruginosin congeners (**48–51**) was achieved by our group, through a convergent approach wherein two important fragments were constructed by Pd-catalyzed $\text{C}(\text{sp}^3)\text{--H}$ functionalization (Scheme 10).^[53] Disconnection of the targets at the three

Scheme 10. Synthesis of aeruginosins by Baudoin and co-workers. TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; Cbz = carboxybenzyl.

amide bonds provided the four fragments **52–55**, containing structural variations on three of them. The most complex, octahydroindole fragment **52** was obtained from alkene precursor **56** by hydrogenation. The latter arose from bromoalkene **57** by Pd⁰-catalyzed C(sp³)-H alkenylation,^[51] similar to the method described above in the synthesis of DTP molecules (Scheme 9), which was performed on multigram scale in ca. 70% yield. In turn, **57** was obtained through a sequence starting with commercially available alcohol **58** and L-alaninol **59**. In parallel, the three hydroxyphenyllactic fragments **54a–c** were synthesized from amides **60a–c** containing the pyridine-based bidentate directing group developed by Shi and co-workers.^[54] Compared to other bidentate directing groups, the latter could be removed under milder conditions, hence avoiding the epimerization of the somewhat sensitive stereocenter. Amides **60a–c** were synthesized via directed palladium(II)-catalyzed C(sp³)-H arylation with the appropriate aryl iodides,^[22] and the corresponding amide precursor was obtained from methyl D-lactate. This method allowed the divergent introduction of various aryl groups, including those substituted with chlorine and bromine atoms, which are present in aeruginosins 98A and 98C (**50–51**). Overall, this synthesis of aeruginosins illustrates the interest of catalytic C–H functionalization for both convergent—easy synthesis of several fragments from the chiral pool—and divergent—easy access to analogous fragments and by extension to several congeners—aspects.

3.2. Convergent syntheses wherein fragments are coupled by C–H functionalization

Transition-metal-catalyzed C–H functionalization has the potential to replace traditional cross-couplings as a transform for the coupling of advanced fragments in a convergent total synthesis. This principle will be illustrated through two examples, which also employ C–H functionalization to build

one of the key fragments. In 2011, Wang and Yu reported the synthesis of (+)-lithospermic acid (**62**),^[10a] a polyphenol constituent of traditional herbal medicine (Scheme 11).^[55] The protected form **63** was disconnected at the highlighted C–C bond via a carboxylic acid-directed palladium(II)-catalyzed C–H alkenylation,^[56] which, similar to the non-directed Fujiwara-Moritani reaction, can be regarded as a halogen-free surrogate of the Mizoroki-Heck cross-coupling.^[57] After optimization, the oxidative coupling of dihydrobenzofuran **64** with olefin **65** was achieved in 93% yield using Pd(OAc)₂/N-acetylisoleucine as the catalyst under one atmosphere of O₂. In turn, olefin **65** was readily obtained from commercially available (*R*)-rosmarinic acid (**66**).

Besides, the furan ring of **64** was built through asymmetric intramolecular C–H carbene insertion from diazo precursor **67**. Achieving a satisfying stereoselectivity (dr 8:1) required the combination of a chiral auxiliary [R* = pyrrolidinyl (*S*)-lactamide]^[58] and Davies' Rh₂(*S*-DOSP)₄ chiral catalyst,^[59] a strategy that was later reused in the previously discussed synthesis of incarvaton A (Scheme 1). Finally, intermediate **67** was obtained in 7 steps from commercial *o*-eugenol **68**. This multiple C–H functionalization strategy allowed a straightforward enantioselective synthesis of (+)-lithospermic acid in 11% yield over 12 steps (longest linear sequence from **68**).^[60]

Another illustration of a C–H functionalization transform employed to couple complex fragments, combined with another C–H functionalization step to access one of these fragments, is furnished by the synthesis of (–)-complanadines A and B (**69–70**) by Tsukano and co-workers.^[61] These molecules are dimeric *Lycopodium* alkaloids that were shown to induce the secretion of neurotrophic factors.^[62] Target molecules **69–70** were obtained from C–H functionalization retron **71**, which was disconnected at the bipyridine bond to give the two monomeric units **72–73**. The corresponding transform was the Fagnou palladium(0)-catalyzed C–H arylation of pyridine *N*-oxides,^[63] which allowed selective

Scheme 11. Synthesis of (+)-lithospermic acid by Wang and Yu.

cross-coupling with bromopyridine **73** at the free *ortho* position of the *N*-oxide in **72**. This method can be regarded as a surrogate of a Suzuki–Miyaura or related cross-coupling.^[64] Its adaptation to the current substrates required optimization, which included the use of the bulky *t*-Bu-DavePhos [2-di-*tert*-butylphosphino-2'-(*N,N*-dimethylamino)biphenyl] ligand to achieve a useful yield (62 %). In addition, an excess of *N*-oxide **72** (2 equiv) was necessary, but it could be partially recovered. Fragments **72** and **73** were then obtained from the same enantiopure precursor **74**. In particular, the bromine atom in pyridine **73** was site-selectively introduced through iridium-catalyzed C–H borylation^[6] and copper-mediated bromination,^[7] a method which was already discussed in the context of the synthesis of incarviate A (Scheme 1), and employed earlier in the Sarpong synthesis of complanadine A.^[64] Enantiopure (+)-**74** was obtained by resolution of the racemic mixture by HPLC on a chiral stationary phase. This racemic compound was an intermediate in the synthesis of (±)-lycodine, previously reported by Tsukano, Hiramata and co-workers,^[65] and was obtained in 14 steps from heterocyclic precursors **75–76**.

Scheme 12. Synthesis of (–)-complanadines A and B by Tsukano and co-workers.

4. Conclusion

In the past decade, multiple transition-metal-catalyzed C–H functionalization has emerged as a powerful approach to streamline the synthesis of natural products. In this Minireview, several aspects were presented: sequential C–H functionalization from a cyclic core, late-stage multiple C–H functionalization, construction of polycyclic systems via multiple C–H functionalization, and multiple C–H functionalization in convergent synthesis. C–H activation methods are flourishing and are contributing to reshape retrosynthetic analysis by providing new bond disconnections from more available precursors. Importantly, natural products are pro-

totypical complex molecules, and the highlighted cases could inspire medicinal and process chemists in their efforts to construct and diversify bioactive molecules using C–H functionalization logics. Moreover, these logics are also useful to streamline the access to functional organic materials.^[66] Therefore, (multiple) catalytic C–H functionalization should be a key contributor to the sustainable synthesis of functional molecules in the years to come.

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Conflict of interest

The authors declare no conflict of interest.

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