Use of Emerging C–H Functionalization Methods to Implement Strategies for the Divergent Total Syntheses of Bridged Polycyclic Natural Products

Goh Sennari^{1,2}* and Richmond Sarpong¹*

¹Department of Chemistry, University of California–Berkeley, Berkeley, California 94720, United States ²Ōmura Satoshi Memorial Institute and Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan. E-mail: sennari.go@kitasato-u.ac.jp, rsarpong@berkeley.edu

Abstract: Carbon-hydrogen (C-H) bonds are ubiquitous in complex natural products. Over the past three decades, many methods to convert C-H bonds distal from functional groups, which were generally considered inert, have been developed. These advances now enable selective peripheral functionalizations at a late-stage. The direct engagement of traditionally unreactive C-H bonds in reactions expands chemical space by reducing functional group interconversions. As such, C-H functionalization serves as a powerful tool in medicinal and agrochemical chemistry as well as in the total synthesis of natural products where diversification to a broad array of compounds from a common intermediate is often desired. In this Account, we detail the thought processes and design principles that relied on emerging methods for C-H functionalization to prepare a wide range of bridged, polycyclic, natural products in the cephalotane and longibornane families from a common intermediate in each case.

1. Introduction

Over the last century, architecturally complex natural products have inspired synthetic chemists to develop strategies and new methodologies to accomplish their practical preparation. Total synthesis of natural products, which are often secondary metabolites isolated from microorganisms, has historically served as a means to elucidate unambiguously the structure of the natural product. In addition, total synthesis has provided larger amounts of a target natural product and derivatives to aid investigations of function including biological activity. Finally, total synthesis endeavors have provided an opportunity to showcase the power of new chemical transformations and expose their limitations.1 Central to the exercise of a total synthesis is identifying an efficient plan to access the structural complexity of a target molecule from readily available building blocks.² In this regard, exploring the use of existing chemical reactions along with the invention of new reactions to implement a planned approach (strategy) is critical.

One attractive approach toward crafting complex natural products is to employ transformations that are used in the biosynthesis of the target molecule.3 Collectively, studies in the field of isolation and characterization of secondary metabolites indicate that ring-forging events, followed by functionalizations of the carbon framework in a selective and functional group tolerant manner, often feature in the biosynthesis of secondary metabolites.⁴ As such, strategies for total synthesis inspired by biosynthesis pathways have proved invaluable in chemical synthesis. Two terms are usually associated with such strategies. The first is "biomimetic" synthesis, whereby the laboratory synthetic plan imitates the biosynthesis process.⁵ In this case, reagents and conditions that mimic those employed in the biosynthesis are used. The second term that is often used is "bioinspired" synthesis. In this case, the insights from a biosynthesis pathway guide the development of a synthetic plan.⁶ We have been interested in this latter synthetic approach with the goal of highlighting designs for natural product synthesis broadly inspired by their biosynthesis.7 This Account details our recent realization of bioinspired two-phase strategies for synthesis of two families of natural products.8

Terpenoids, which are the largest class of natural products, feature a wide variety of core-scaffolds with numerous functionalities and therefore cover a broad range of chemical space.9 Despite their varied architectures and functional groupings, the biosynthesis machinery employs a two-phase strategy for their syntheses as recently highlighted by Baran and coworkers (Figure 1).10 First, linear hydrocarbons consisting of isoprene subunits and a phosphate group undergo various enzyme-controlled cyclization and rearrangement events.11 This highly orchestrated cyclase phase constructs various core structures in sub-families of terpenoids that are categorized by the number of carbon atoms in the starting pyrophosphate (C10mono-, C₁₅-sesqui-, C₂₀-di-, C₂₅-sester-, and C₃₀-tri-terpenes etc.). Following the cyclase phase, additional enzymatic derivatizations of the generated C(sp³)-H rich cyclic framework proceed typically through stereo- and site-selective oxygenations (referred to as the oxidase phase), to give various terpenoid end products.12



Figure 1. A general depiction of terpenoid two-phase biosynthesis (OPP: diphosphate).

Similar to the diversification of a common carbocycle in the "oxidase phase" that occurs in nature, related tactics to tailor the periphery of a common synthetic intermediate to access various natural products has found much success in chemical synthesis.13 Specifically, recent advancements in C-H functionalization technology has created myriad opportunities for efficient peripheral diversification.14 Selective derivatization of C-H bonds by their direct functionalization reduces functional group Consequently, interconversion steps. selective C-Hfunctionalizations, which have been termed a "holy grail" in chemical synthesis,15 pave a more direct way to a target compound. We envisioned that the rapid construction of the core framework of a target molecule along with the implementation of C-H functionalization methodology would set the stage for efficient total syntheses that would also shed light on the advantages, scope and limitations of the currently available methods for C-H functionalization. Here, we provide details of two total synthesis campaigns-of the cephalotane norditerpenoids^{8a,8d} and longibornane sesquiterpenoids^{8b,8c}which highlight our use of bioinspired two-phase synthetic strategies.

2. Chemical Network Analysis

Key to implementing our two-phase synthesis of natural products in the cephalotane and longibornane families was the identification of a concise, practical and scalable route to a common synthetic intermediate in each case.¹⁰ In the 1960s, Corey and coworkers proposed a logic for chemical synthesis by iteratively simplifying a target or product-relevant structure in the reverse-synthetic (retrosynthetic) sense, back to readily available chemical feedstocks.¹⁶ Since these key contributions by Corey, retrosynthetic (antithetic) analysis has become a generally adopted approach in the synthesis community to aid in the identification of strategies for natural product synthesis. Particularly, for bridged polycyclic compounds, because the basis of the retrosynthetic analysis is to reduce structural complexity, a bond disconnection in the maximally bridged ring (MBR) effectively simplifies the molecule's topology, achieving maximal structural simplification in the retrosynthetic direction.² As a case study, Corey and coworkers applied "strategic bond disconnection" logic to the total synthesis of longifolene (1), which was emblematic of topologically complex natural products in that era (Figure 2A). Following six guidelines,² disconnections "a", "b" and "c" across five C-C bonds in the MBR were deemed to be strategic by chemical network analysis. Subsequently, in the forward sense, Corey et al. demonstrated that an intramolecular Michael addition of keto-enone 2 (possessing a structurally simpler 7-6 fused ring system) guided by disconnection "a" was effective in forging the bridged framework, resulting in a visionary 15-step total synthesis of 1.16

On the basis of Corey's chemical network analysis, our group has identified objective bond disconnections of various structurally complex natural products and used these retrosyntheses as a guide for total synthesis. Historically, bicyclization reactions have proven to be very powerful in natural product total synthesis.¹⁷ For example in their synthesis of longifolene, Johnson and coworkers demonstrated a 13-step total synthesis from a commercially available cyclopentanone

(Figure 2B).¹⁸ In their approach, a formal (3 + 2) cycloadditiontype reaction of monocyclic five-membered alcohol 3 along the lines of disconnections "b" and "d" was employed in a key step. On this basis, it is evident that forging the MBR in natural products by means of a bicyclization would rapidly increase the inherent structural complexity.¹⁹ The cephalotane benzenoids presented an attractive target to demonstrate this type of approach. Alternatively, in stark contrast to Corey's strategic bond disconnection approach where the MBR is disconnected in the retrosynthetic sense, we sought to develop an orthogonal approach in our syntheses of the longifolene-related longibornane sesquiterpenoids. In this case, we envisioned that instead of reducing the structural complexity by removing bridging in our retrosynthesis, retaining the topological complexity of the MBR would provide opportunities to use camphor derivatives as a starting point of the synthesis (Figure 2C). Detailed herein are our syntheses of the cephalotane natural benzenoid products and the longibornane sesquiterpenoids that have at their foundation of the thought processes described in the preceding paragraphs.



Figure 2. Established examples of retrosynthetic analysis in longifolene syntheses and our approach toward syntheses of bridged polycyclic natural products in the cephalotane and longibornane families.

3. Syntheses of the Cephalotane Norditerpenoids

The cephalotane norditerpenoids are a large family of natural products of which more than 80 congeners have been isolated to date.²⁰ The benzenoid congeners, namely cephanolides A–D and ceforalides A–G, were isolated from *Cephalotaxus sinensis* in 2017²¹ and *Cephalotaxus fortune* var. *alpina* in 2022,²² respectively, by Yue and coworkers. The intriguing structures of these molecules, along with their varied oxidation patterns, has drawn the attention of many groups who have undertaken their total synthesis.²³

3-1. Retrosynthesis of the Cephalotane Benzenoids

We envisaged that the disparate oxygenation patterns of the cephanolides and ceforalides could be installed selectively by exploiting C-H functionalizations of the arene moiety and the activated benzylic positions at a late-stage. In principle, this approach equates to the oxidase phase in biosynthetic logic. In this regard, the hypothetically least-oxidized intermediate (4) was selected as a common precursor for late-stage diversification and became the target of an initial cyclaseinspired phase (Figure 3). Chemical network analysis reveals the [2.2.2] bicycle of 4 as the structurally most complex region of the molecule. Keeping in mind bicyclizations as an effective means to achieve rapid increases in structural complexity, we envisioned constructing the [2.2.2] bicycle of 4 using an intramolecular inverse-electron-demand Diels-Alder (IEDDA) reaction of indene-pyrone 5. It was our expectation that this cycloaddition would be endo-selective.24 We rationalized that compound 5 could be prepared through a coupling sequence using readily available indanone 6 and pyrone derivatives 7, which would be tethered by a two-carbon building block.



Figure 3. Our retrosynthesis of the cephalotane benzenoids.

3-2. Investigation of the Synthetic Cyclase Phase

Our synthesis of the cephalotanes began with triflation of commercially available hydroxy indanone 6, providing triflate 8 (Scheme 1). For ease of preparation, the ensuing coupling sequence was initially attempted using pyrone triflate 7b as a coupling partner.25 We found that the iterative cross-coupling conditions reported by Molander and coworkers²⁶ were effective for this purpose. Treatment of 8 with borane reagent 9 under Pdcatalyzed conditions afforded homologated indanone 10, which was then subjected to a second Pd-catalyzed cross-coupling with pyrone 7b to give rise to the desired product (11) in good yield over two steps (or moderate yield in one-pot). Reduction of the ketone carbonyl group and subsequent elimination of the resulting hydroxy group under the acidic conditions afforded indene 12 in good yield. With the desired precursor for the key cycloaddition in our planned cyclase phase in hand, we attempted a variety of conditions to promote the IEDDA cycloaddition.27 Ultimately, although we obtained desired cycloadduct 13 stereoselectively, we experienced several issues. For example, despite screening various activating agents, the indene moiety in 12 was not sufficiently reactive and the cycloaddition only proceeded with thermal heating. However, upon heating, competing aromatization of the product (13) via decarboxylation occurred, therefore giving cycloadduct 13 in only moderate yield (up to 58% yield).





On the basis of the observations described above, we sought to enhance the reactivity of the indene portion of the IEDDA substrate through HOMO raising. In this regard, indanone **11** was subjected to soft-enolization conditions using TMSOTf in the presence of DIPEA to access TMS-enol ether **14**. Fortunately, under the soft enolization conditions, spontaneous cycloaddition was observed, giving rise to desired cycloadduct **15** in 80% yield as a single diastereomer. This success led us to explore cycloaddition of the substrate bearing a methyl group at the pyrone C4-position, which would result in direct construction of the core structure in the cephalotane benzenoid family.

For this purpose, indanone **16** was prepared in a similar manner from **8** by iterative cross-coupling using pyrone triflate **7a**. With **16** in hand, we investigated the intramolecular cycloaddition. However, in this case, we did not observe the formation of cycloadduct **19** under any of the conditions that were explored. Instead, for instance, treatment of **16** with the conditions that led to cycloadduct **15** forged an eight-membered ring presumably through an intramolecular vinylogous

Mukaiyama-type aldol reaction, likely via silyl ketene acetal **17**, affording **18** in 24% yield along with accompanying nonspecific decomposition. Because this more direct construction of the fully elaborated core was unsuccessful, it necessitated an installation of a methyl group on the double bond of cycloadduct **15**. We elected to explore downstream peripheral tailoring using **15** as the common synthetic intermediate.

3-3. Strategy for Late-Stage Diversification

To gain access to a broad range of congeners in the cephalotane benzenoid family, we recognized two major challenges for peripheral C-H functionalization. First, we would need to select for oxidation at one of the two similarly reactive benzylic methylene C(sp3)-H bonds at C7 and C20. Second, site selective functionalization of the arene C(sp²)-H groups at C13 and C15 would need to be achieved (Figure 4). To achieve selective benzylic oxidation, we postulated that because the C7 position would be more sterically accessible than C20, undirected oxidation might differentiate these two positions (see A). On the other hand, the hydroxy group at C3 could direct oxidation at C20 through a 1,5-hydrogen-atom-transfer (HAT) process induced by the generation of an alkoxy radical (see B).28 Toward a selective arene C-H functionalization, we anticipated that undirected oxygenation would functionalize C13 due to the inductive effect of the proximal oxygen functional groups (see C). Instead, installation of a directing group at C7 could facilitate ortho-C-H metalation, enabling functionalization at C15 (see **D**).²⁹ With these thoughts in mind, we undertook an investigation of the "oxidase phase" of our syntheses of the cephalotanes.



Figure 4. Strategy for the late-stage diversification of the cephalotane benzenoid core (DG: directing group).

3-4. *En Route* to Cephanolides B–D through Formal Hydromethylation of the Common Intermediate

A remaining task to construct the complete core-scaffold of the cephalotane benzenoids from cycloadduct **15** was an

installation of the methyl group at the C4 position. We turned our attention to alkene difunctionalization methods that enable methylative introduction of a functional group across double bonds. As a result of our extensive screening and optimization, we found that borocupration of the double bond powerfully served this purpose (Scheme 2). Subjection of 15 to the borocupration conditions reported by Fu and coworkers³⁰ and subsequent electrophilic trapping of the resulting sp3organocopper species with MeI gave rise to methyl Bpin ester 20 in 83% yield as a single isomer. Next, following the protocol reported by Studer and coworkers,³¹ photoinduced protodeboronation effected a formal hydromethylation of common intermediate 15. Treatment of 20 with PhLi to form borate 21, followed by Ir-catalyzed photoredox conditions in the presence of PhSH effected deborylation, which along with cleavage of the TMS group afforded alcohol 22 in good yield. Deoxygenation of the tertiary hydroxy group in 22 using In-catalyzed ionic reduction conditions³² gave pentacycle 23, which was subjected to phthaloyl peroxide-mediated oxygenation conditions reported by Siegel and coworkers³³ to complete the total synthesis of cephanolide B. The synthesis proceeded in seven steps from the commercially available starting material. Although the selectivity in the final arene oxygenation step was modest, we note that the constitutional isomer of cephanolide B, which has not been found in nature, was also synthesized through this approach, highlighting the power of the two-phase strategy to explore adjacent chemical space.

Scheme 2. Synthesis of cephanolide B using methyl boration as the key transformation.



The formal hydromethylation of common intermediate **15** that we established for the synthesis of cephanolide B provided opportunities to gain access to other congeners (Scheme 3). An undirected oxidation of the benzylic methylene group in **22** using PCC gave rise to cephanolide C in acceptable yield (overall six steps). To explore our planned directed *ortho*-C–H functionalization chemistry, the ketone carbonyl group of cephanolide C was converted to a directing methyl oxime group (see **24**). We found that Rh-catalyzed methyl oxime-directed $C(sp^2)$ –H cyanation³⁴ of **24** successfully afforded the desired

nitrile (25) in good yield. Unfortunately, conversion of the cyano group in 25 to a methyl ester in the presence of the [2.2.2] bicyclic δ -lactone moiety was extremely challenging. To circumvent this issue, we explored a more direct way to install a methoxycarbonyl group. Directed *ortho*-C–H palladation followed by methoxycarbonylation³⁵ was found to be effective, providing the desired methyl ester (26) in moderate yield. Finally, removal of the methyl oxime in 26 using ozonolysis³⁶ gave cephanolide D (nine steps overall).

Scheme 3. Synthesis of cephanolides C and D through relay C– H functionalization.



3-5. Syntheses of Cephanolide A and Ceforalides

As described above, the methyl boration/protodeboronation sequence (formal hydromethylation) allowed access to cephanolides B–D. We were optimistic that the alkene difunctionalization approach of common intermediate **15** could also facilitate synthesis of C3 oxidized congeners (Scheme 4).

To this end, common intermediate **15** was subjected to the methyl boration conditions, followed by one-pot oxidation of the resulting Bpin ester, affording methyl alcohol **27** in 77% yield as a single isomer. The hydroxy group in **27** was oxidized using the Jones reagent which was accompanied by acid-promoted cleavage of the TMS group to provide keto-alcohol **28**. Deoxygenation of the tertiary hydroxy group in **28** was conducted by a two-step protocol—bromination³⁷ and subsequent reductive radical dehalogenation. This was followed by diastereoselective reduction of the ketone carbonyl group to give ceforalide D in eight total steps from commercially available indanone **6**.

Our approach set the stage to showcase modern C-H oxidation technologies to achieve selective benzylic oxidation of the chemically similar methylene C(sp³)-H bonds at C7 and C20 in ceforalide D. Although PCC-mediated oxidation conditions were effective in oxidizing the benzylic methylene C-H bonds en route to cephanolide C (see Scheme 3), we aspired to a selective C7 oxidation in the presence of the unprotected secondary hydroxy group. Ultimately, following extensive optimization, we found that photoinduced conditions using iodosobenzoic acid (IBA) as an oxidant³⁸ gave rise to the desired product directly without the need for any protecting groups. In this way, ceforalide C was synthesized in a total of nine steps. On the other hand, selective C20 methylene oxidation was achieved by the alcohol-directed 1,5-HAT³⁹ to give hexacycle 30 in excellent yield. Subsequent C7 oxidation of 30 using PCC gave rise to ceforalide F in a total of 10 steps.

With our success in discriminating between the reactivity of the benzylic positions of the cephalotane family, the final remaining task was to achieve selective $C(sp^2)$ –H functionalization at C13. Toward this goal, we attempted a variety of conditions for arene C–H functionalization.^{33,40} In comparison to the cephanolide B precursor (**23**), direct oxygenation of **30** turned out to be more challenging, presumably due to the activated methine C–H bond at C20. Our

Scheme 4. Divergent synthesis of cephanolide A and ceforalides by selective benzylic oxidation and arene C-H functionalization.



efforts to install a functional group that can be converted to the hydroxy group led to the identification of the Ritter C–H thianthrenation⁴¹ reaction. Treatment of **30** with tetrafluoro-thianthrene *S*-oxide (TFTO) gave rise to the desired TFT salt (**31**) in quantitative yield and good C13 selectivity. Photoinduced conversion of **31** to the corresponding Bpin ester and subsequent oxidation afforded the desired phenol in excellent yield. This sequence was effective in a one-pot manner, completing the total synthesis of cephanolide A in 10 total steps. Furthermore, we found that selective C7 benzylic hydroxylation of Bpin ester **32** was possible by employing photo-mediated conditions,³⁸ followed by oxidation to provide ceforalide G in a total of 13 steps.

So far in this Account, we have showcased divergent syntheses of cephalotane natural products using a two-phase strategy. Our work enabled access to eight cephalotane benzenoid congeners. This strategy also laid the foundation for the synthesis of additional cephalotane congeners, which has been pursued in the Sarpong group. Overall, our syntheses of the cephalotanes highlight selective manipulations of relatively activated benzylic and arene C–H bonds in the bioinspired C–H functionalization oxidase phase. In contrast, *en route* to the synthesis of the longibornane natural products, we relied on functionalization of unactivated alkyl C(sp³)–H bonds as described hereafter.

4. Synthetic Study of Longibornane Sesquiterpenoids

The longibornane and the biosynthetically related longifolane sesquiterpenoids, which were first reported in the mid 1900s, comprise some of the most iconic natural products discovered to date.⁴² Despite their architectural similarity, synthetic studies of the longibornanes⁴³ has been less explored than that of longifolene (1).^{16,18,43c,43d,44} Since the isolation of longiborneol, various oxidized congeners have been reported,⁴⁵ prompting us to develop a two-phase synthetic strategy to access a wide range of natural products in this family.

4-1. Retrosynthesis of the Longibornane Sesquiterpenoids

We envisioned that the various oxidized congeners in this family-namely hydroxylongiborneols, (hydroxy)culmorins, and culmorone-could be ultimately derived from longicamphor (33) by site-selective C(sp³)–H oxidation (Figure 5). As opposed to classic bond disconnection logic, we sought to construct the tricyclic core of 33 using a polarity-reversal cyclization of the tertiary radical (34) generated by metal-hydride hydrogen-atomtransfer (MHAT) from alkene 35, which could forge the sevenmembered ring through the addition into an enol-derived double bond. In this case, the generated nucleophilic tertiary radical from the exomethylene group in 35 is polarity mismatched with the electron-rich enol double bond, making the planned radical addition kinetically unfavorable. We hypothesized that this potential challenge could be resolved by using electron-poor enol derivatives along with the choice of leaving groups (X group in 34) to tune the stability of the radical that results after scission of the C-X bond.

Compound **35** was envisioned to arise from a functionalized camphor derivative^{43c,43d,46} such as **36** by homologation. Overall, this plan retains the topology of the maximally bridged ring in the retrosynthetic simplification process. In this analysis, the

structural complexity would not be drastically reduced as compared to the classic strategic bond disconnection approach. However, because both enantiomers of camphor and related derivatives are readily available chemical feedstocks, we believed that we could gain ready access to the required core structure of the longibornanes and in this way accomplish an efficient synthesis that rests on a logic that is orthogonal to Corey's chemical network analysis.



Figure 5. Our retrosynthesis of longibornane sesquiterpenoids.

4-2. Investigation of the Synthetic Cyclase Phase

Our synthesis of the longibornanes began with a scaffoldremodeling of (S)-carvone (**37**) to access a functionalized camphor (Scheme 5).⁴⁶ Epoxidation of **37** using *m*-CPBA and subsequent Ti(III)-mediated reductive cyclization via tertiary radical **38**⁴⁷ afforded diol **39**, which was treated with TsOH to promote a semi-pinacol rearrangement, providing hydroxycamphor **40** in good yield. The hydroxy group in **40** was oxidized using TEMPO-PIDA conditions in the presence of AcOH to afford aldehyde **41**, followed by homologation using a Wittig olefination to give skipped diene **42** in good yield as a single double bond diastereoisomer. We prepared several enol derivatives (**43**) by treating **42** with a strong base to generate the corresponding enolates followed by trapping with an electrophile in preparation for the radical cyclization step.



Scheme 5. Preparation of the radical cyclization precursors.



Figure 6. Development of the MHAT radical cyclization.

With the enol derivatives (see 43) in hand, we attempted radical cyclization under Fe-mediated MHAT conditions (Figure 6).⁴⁸ In entry 1, although silvl enol ethers are often employed as electron-rich acceptors in coupling with electrophilic radicals,49 we rationalized that generation of the stabilized silvl radical would be a driving force for the cyclization of 43a. Unfortunately, in this case, the reaction gave a complex mixture, presumably due to competitive HAT to the silvl enol ether moiety.50 We then employed enol phosphate 43b (entry 2), which would generate a stabilized phosphite radical⁵¹ after cyclization and O-P bond scission. However, in this case, only nonspecific decomposition was observed. Next, when vinyl pivalate 43c was subjected to the MHAT conditions (entry 3), we obtained tetracycle 45 in 51% yield. In this case, although the sevenmembered ring-forming event proceeded, the resulting α -oxy radical underwent 5-exo-trig cyclization with the neighboring double bond instead of the desired decarbonylation to generate a *tert*-butyl radical. Subjection of vinyl carbonate **43d** to the reaction conditions (entry 4), with the aim of generating a radical after the initial cyclization that would undergo decarboxylation to release the stabilized *tert*-butyl radical, also afforded tetracycle **46** in 52% yield.

Given that a competing, undesired, C-C bond formation outcompeted O-C bond scission in many of our attempted seven-membered ring forming reactions (Figure 6, entries 3 and 4), we turned our attention to enol derivatives with weaker heteroatom-oxygen bond. In this regard, treatment of vinyl nonaflate 43e with the MHAT conditions (entry 5) gave rise to fluoroalkyl adduct 47 in 51% as a single diastereomer along with a trace amount of the desired product (44). This result suggested that following the desired cyclization and O-S bond scission, the resulting sulfonyl radical underwent desulfonation and the generated electrophilic perfluoroalkyl radical then engaged the electron-rich double bond⁵² of the starting material (43e) to propagate the radical chain process. On the basis of this undesired but informative result, we postulated that an aryl sulfonate group could suppress desulfonation after the O-S scission due to the enthalpic barrier associated with generating a high energy aryl radical species. To this end, vinyl tosylate 43f was subjected to the radical cyclization conditions, affording desired tricycle 44 as the sole observed product in 60% yield. Using this novel MHAT cyclization, we were able to construct the carboskeleton of the longibornane family.

4-3. Total Synthesis of Longiborneol and Longifolene

Over the course of optimizing our preparation of vinyl sulfonates and the subsequent MHAT radical cyclization, we found that instead of vinyl tosylate **43f**, the corresponding phenyl sulfonyl group was superior for both reactions (Scheme 6). Treatment of **42** with NaHMDS and (PhSO₂)₂O gave vinyl sulfonate **43g**, which was subjected to the MHAT conditions in the presence of buffering reagents, affording tricycle **44** in excellent yield. Hydrogenation of the double bond in **44** to provide longicamphor (**33**), followed by dissolving-metal-medi-

Scheme 6. Endgame of the longiborneol synthesis and rearrangement to longifolene.



ated diastereoselective reduction of the carbonyl group in **33** gave rise to longiborneol in good yield. Overall, the synthesis of longiborneol proceeded in a total of nine steps on multigram scale. In addition, we found that treatment of longiborneol with a chlorosulfonamide promoted a Wagner–Meerwein rearrangement (via a presumed non-classical carbocation) to give longifolene (1) in good yield. Using this approach, we synthesized (–)-longifolene (1) in a total of 10 steps—the shortest to date from commercially available starting materials.

4-4. Exploration of the Oxidase Phase

With a route established for the synthesis of the longibornane core, we proceeded to investigate late-stage diversification en route to congeners in this sesquiterpenoid family (Figure 7). Because the longibornane core is a C(sp³)-H-rich carboskeleton with only one functional group, we anticipated that selective manipulation of the C-H bonds might be very challenging. To gain access to oxidized congeners of this family, we required a way to distinguish three methyl and methylene sites in C-H functionalizations. We hypothesized that undirected oxidation would proceed at the more accessible non-neopentyl methylene groups at C4 and C11 (see A). Generally, this type of reaction proceeds through hydrogen atom abstraction of the more electron-rich hydridic C-H bond and capture of the resulting Ccentered radical.53 Therefore, methine C-H bonds are usually more susceptible to oxidation over primary and secondary C-H bonds.^{12c,54} In our case, we thought that the C7 methine could be deactivated toward C-H abstraction by the inductive effect of the vicinal oxygen functional group. In addition, the C-H abstraction at C1 might be disfavored as the C-H bond resides at a bridgehead position that would lead to a relatively unstable, pyramidalized radical.

Using the resident functional group in **33** to direct selective C–H functionalization, we rationalized that installation of a directing group at C8 would allow functionalization of the methyl group at C12 and/or C15 (see **B**). Complementary to the



Figure 7. Strategy for the late-stage diversification of the longibornane natural products (DG: directing group).

radical-based transformations, C–H metalation provides opportunities to selectively functionalize primary C–H bonds because steric encumbrance often limits C–H activation at more hindered positions.⁵⁵ In a related strategy, we envisioned that the hydroxy group of longiborneol or its epimer could direct functionalization that would ultimately yield C3, C5 and/or C15 oxidized congeners (*vide infra*).⁵⁶

In addition to the C–H functionalization of saturated longibornane derivatives, we sought to utilize **44**, possessing an additional functional handle, to effect diversification on the seven-membered ring. The double bond of **44** would facilitate oxygenation at C3 by hydration-type reactions and at C5 by allylic oxidation for the preparation of oxidized congeners. Furthermore, we anticipated that newly installed functional groups at C5 using the alkene group of **44** would direct C–H oxidation at C14 and/or C15 through a relay C–H functionalization strategy (see C).

4-5. Total Synthesis of Culmorone and Culmorin Using Undirected C-H Oxidation

To achieve site selectivity in the planned undirected C-H oxidations, we sought to install an electron-withdrawing group on the hydroxy group of longiborneol (Scheme 7). In this regard, longiborneol was treated with Ac2O, affording acetate 48, which was subjected to various undirected C-H oxidation tactics. As a result of our extensive screening and optimization,53,54,57 we found that the Ru-catalyzed conditions reported by Du Bois, Sigman and coworkers⁵⁸ gave the best result with a good mass balance, providing ketone 49 as a major product in 54% NMR yield. Additionally, we obtained C3- and C5-oxidized ketones 50 (9% NMR yield) and 51 (10% NMR yield), along with the desired C11 ketone (52) in 10% NMR yield. Through our investigation of undirected oxidation, we observed that in the longibornane core structure, the C4 position is the most accessible and thus prone to facile oxidation, while other positions such as C3, C5 and C11 react similarly under oxidation

Scheme 7. Undirected C–H oxidation-enabled syntheses of culmorone and culmorin.



conditions. Although the overall reaction profile indicated a less selective process than had been anticipated, our scalable synthetic route gave us the opportunity to complete total syntheses of the natural product targets.

Following the Ru-catalyzed oxidation, due to the difficulty in separating C11 ketone **52** from **51**, the mixture was subjected to acetyl cleavage conditions to give the corresponding alcohols, which were separated at this stage. Consequently, culmorone was synthesized in overall 11 steps from the commercially available (*S*)-carvone. Furthermore, dissolving-metal-mediated diastereoselective reduction of the carbonyl group in culmorone gave rise to culmorin in good yield. In this way, albeit modestly selective, we achieved a total synthesis of culmorin in a total of 12 steps.

4-6. Directed C–H Functionalization Approach *En Route* to 12-Hydroxylongiborneol

We first sought to use the hydroxy group of longiborneol or its epimer for remote C–H functionalization through 1,5-HAT (Figure 8).²⁸ Conformationally, it was envisioned that the pseudo axially disposed hydroxy group could direct C15 C–H functionalization (see **D**), whereas hydrogens at C3 or C5 positions might be abstracted by the pseudo equatorial alkoxy radical (see **E**). This strategy, however, turned out to be challenging presumably due to the strain inherent in the [2.2.1] bicycle which accelerates a competitive β -scission instead of 1,5-HAT, resulting in nonspecific decomposition (see **F**).



Figure 8. Strategy and challenge for remote C–H oxidation using the hydroxy group.

We then turned our attention to oxime-directed C–H palladation chemistry (Scheme 8).⁵⁹ We thought that C8 oximes derived from either ketone **33** or **44** would be an ideal directing group to effect C–H acetoxylation at C12 via the corresponding five-membered palladacycle. Unfortunately, despite our extensive efforts to condense a methoxy amine or hydroxy amine onto **33** or **44**, the desired oxime was not observed under any conditions. We rationalized that the extreme steric encumbrance around the carbonyl group in these substrates, likely attributed to the neopentyl position and proximity to the quaternary center, thwarted our efforts to achieve condensation.

On the basis of the challenges described above, we sought to explore other C–H metalation reactions that could be promoted by alcohol-derived directing groups. In this regard, we were drawn to Hartwig C–H silylation chemistry⁶⁰ using oxysilanes prepared from the corresponding alcohols. Because of our preliminary result that longiborneol-derived silanes were not effective substrates for C–H silylation, we prepared alcohol **53** quantitatively by diastereoselective reduction of the carbonyl

group in **33**. Treatment of **53** with Me₂SiHCl in the presence of Et₃N afforded silane **54**, which was subjected to C–H silylation conditions using an Ir catalyst to provide silacycle **55**. Tamao–Fleming oxidation⁶¹ of **55** successfully afforded the desired diol (**56**) in 70% yield over three steps. The required stereo inversion at C8 to yield the natural product was implemented by a two-step sequence. Global oxidation of diol **56** using DMP afforded keto aldehyde **57**, which was then subjected to the dissolving-metal mediated reduction conditions to provide the desired diol. Overall, the total synthesis of 12-hydroxylongiborneol was achieved in 14 total steps.

Scheme 8. Synthesis of 12-hydroxylongiborneol using directed C–H silylation.



4-7. Diversification of a Key Synthetic Intermediate

Our limited capability to use the saturated longibornane derivatives for selective C–H oxidations led us to take advantage of the unsaturated intermediate (i.e., bearing an alkene group) to complete total syntheses in this family. As described earlier, we envisioned that selective transformation using alkene **44** should provide access to oxidized congeners (Scheme 9). We found that Mukaiyama hydration⁶² of the double bond in **44** provided the corresponding keto alcohol with high stereo and regioselectivity, likely dictated by functionalization on the less sterically encumbered face. Subsequently, diastereoselective reduction of the ketone group yielded the diol in 81% yield over two steps. Overall, this route afforded 3-hydroxylongiborneol in a total of nine steps, highlighting the versatility of alkene **44** as a synthetic intermediate to access adjacent chemical space.

On the other hand, treatment of 44 with SeO₂ gave allylic alcohol 58 as a single diastereomer, whereby oxidation likely occurred from the sterically less hindered face. Hydrogenation of 58 and subsequent dissolving-metal reduction afforded 5hydroxylongiborneol in 10 total steps from (*S*)-carvone. We en-

Scheme 9. *En route* to 3- and 5-hydroxylongiborneol as well as 5-hydroxyculmorin by diversification of intermediate **44**.



visioned 5-hydroxylongiborneol serving as an intermediate to synthesize a higher oxidation state congener building on the insights gained during our undirected C-H oxidation studies. In Scheme 7, we describe the outcomes of undirected oxidation, which occurs predominantly at C4 along with minor oxidation at C3 and C5. We reasoned that installation of an electronwithdrawing group on the hydroxy group at C5 would deactivate the methylene groups on the seven-membered ring toward undirected C-H oxidation. Therefore, global acetylation of the hydroxy groups of 5-hydroxylongiborneol was carried out to give diacetate 59 in good yield. To our delight, we found that TFDO-mediated oxidation⁵⁴ of **59** was the most effective conditions,^{53,57,58} resulting primarily in C11 oxidation. Finally, diastereoselective reduction using dissolving-metal-mediated conditions provided 5-hydroxyculmorin in 13 total steps. The tunable selectivity of the C-H oxidation showcases the power of the rational design of substrates along with the choice of emerging methods to overcome challenges associated with intrinsic reactivities in C–H oxidation reactions.

4-8. Relay C–H Oxidation Tactics *En Route* to 14- and 15-Hydroxylongiborneols.

At this stage, the remaining site-selective C-H bond functionalizations to access other natural products was on the geminal dimethyl moiety in the seven-membered ring of the longibornane skeleton. Our failures to functionalize the C15 methyl group using the C8 hydroxy group through 1,5-HAT or Hartwig silvlation necessitated an alternative approach. We reasoned that relay C-H functionalization using a newly installed directing group at C5, which would be introduced by allylic oxidation, could direct metalation at C14 and/or C15 (Scheme 10). Toward this end, ketone 44 was subjected to diastereoselective reduction, followed by acetylation to afford unsaturated acetate 60 in good yield. SeO2-mediated allylic oxidation of 60 gave alcohol 61 in 92% yield. The double bond in 61 was reduced by hydrogenation, and subsequent oxidation of the hydroxy group using DMP afforded ketone 62 in excellent yield. Condensation of 62 with a hydroxy amine and one-pot acetylation of the corresponding oxime gave rise to acetyl oxime 63, in which the oxime moiety served as a directing group for C-H palladation.59

With precursor 63 for C-H functionalization at C14 and/or C15 in hand, we attempted a wide variety of conditions to effect acetoxylation at these sites. Under the conditions that were explored, both C14 and C15 were prone to react under the palladation conditions, resulting in a competitive second C-H acetoxylation of the desired mono acetate (64). Eventually, we found conditions to suppress overreaction, leading to 64 in acceptable yield as a 2:1 mixture of the diastereomers. Subjection of the mixture of 64 to reductive oxime cleavage conditions⁶³ using Fe in the presence of AcOH and TMSCl afforded ketone 65 as a mixture of diastereomers. Condensation of 65 with tosylhydrazine and subsequent Caglioti reduction⁶⁴ using LAH afforded the natural products, which were separable at this stage. Using this relay strategy, 14- and 15hydroxylongiborneols were each synthesized in a total of 17 steps from (S)-carvone, respectively.





5. Conclusion and Outlook

In this Account, we described our recent studies aimed at divergent natural product syntheses using a bioinspired twophase strategy. Key to the success of our plans was the rapid and scalable construction of the core skeleton for each of the natural product families. For the cephalotane norterpenoids, we used chemical network analysis to rapidly reduce structural complexity in the retrosynthetic direction. Alternatively, for the synthesis of the longibornanes, we adopted an orthogonal approach that retained the complex topology of the core framework, which was prepared from readily available camphor derivatives.

To achieve late-stage diversification, we demonstrated the power of modern C–H functionalizations, which enabled site selective oxidation of key late-stage intermediates. In the synthesis of the benzenoid cephalotane natural products, discrimination of two similarly reactive benzylic methylene groups and two arene C–H bonds allowed access to a variety of the congeners. In the synthesis of the longibornanes, we employed various emerging methods to functionalize typically inert C(sp³)–H bonds. C–H functionalization methods including directed 1,5-HAT mediated oxidation, undirected oxidation including photoinduced methods, arene oxygenation, thianthrenation, directed silylation and palladation were critical to the success of the syntheses described here.

Although challenges such as the requirement for directing groups and inherent substrate reactivity bias still plague the application of C–H functionalization in complex molecule synthesis, the bioinspired two-phase strategy described here enabled divergent total syntheses of two natural product families. Of note, even the undesired products generated by poor selectivity in the C–H functionalizations as well as all synthetic intermediates provide natural product-like derivatives that may provide opportunities to realize new bioactivity. Late-stage functionalization reactions such as those highlighted here effectively expand chemical space beyond what nature might provide. We hope that this work will inspire further developments in the application of late-stage C–H functionalization to natural product synthesis as well as other new innovative methodologies.

Acknowledgements

The authors are grateful to the members of the Sarpong group that contributed to this work, including: Dr. Maximilian Haider, Dr. Stefan Wiesler, Kristen E. Gardner, as well as Alina Eggert on the cephanolide project and Dr. Robert F. Lusi on the longibornane project. G.S. thanks the Uehara Memorial Foundation for a postdoctoral fellowship. The authors thank the NSF under the CCI Center for Selective C–H functionalization (CHE-1700982) and the National Science Foundation (CHE-18566228) for support. We thank the National Institutes of Health (NIGMS MIRA R35 GM130345) for grant support and the Molecular Scaffold Design Collective (Agreement No. HR00111890024) of the Defense Advanced Research Projects Agency for partial support of the work on the longiborneol molecules.

Profile

Goh Sennari received his Ph.D. from Kitasato University in 2018. During that time, he carried out research with Professor Toshiaki Sunazuka. After two years as a postdoctoral fellow with Professor Richmond Sarpong, he assumed the position of Assistant



Project Scientist at the University of California, Berkeley. In 2022, he became an Assistant Professor at Kitasato University in the group of Professor Tomoyasu Hirose and Professor Toshiaki Sunazuka. His research focuses on total syntheses of bioactive natural products and the development of new synthetic methods to derivatize complex molecules.

Richmond Sarpong received his Ph.D. from Princeton University in 2000, supervised by Professor Martin F. Semmelhack. After three and a half years as a postdoctoral fellow with Professor Brian Stoltz at the California Institute of Technology, he started his



independent career at the University of California, Berkeley in 2004 and is at present Professor of Chemistry. His research interests include the development of new strategies for the synthesis of complex natural products and new methods for skeletal editing.

References

- (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. Angew. Chem. Int. Ed. 2000, 39, 44. (b) Wender, P. A.; Miller, B. L. Nature 2009, 460, 197. (c) Hoffmann, R. W. Angew. Chem. Int. Ed. 2013, 52, 123.
- 2) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, G. J. Am. Chem. Soc. 1975, 97, 6116.
- 3) (a) de la Torre, M. C.; Sierra, M. A. Angew. Chem. Int. Ed. 2004, 43, 160. (b) Razzak, M.; De Brabander, J. K. Nat. Chem. Biol. 2011, 7, 865. (c) Bao, R.; Zhang, H.; Tang, Y. Acc. Chem. Res. 2021, 54, 3720.
- 4) Baunach, M.; Franke, J.; Hertweck, C. Angew. Chem. Int. Ed. 2015, 54, 2604.
- (a) Gravel, E.; Poupon, E. *Eur. J. Org. Chem.* **2008**, *2008*, 27. (b) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254.
 (c) Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32.
- 6) (a) Ma, Z.; Chen, C. J. Chin. Chem. Soc. 2018, 65, 43. (b) Zhao, Y.; Long, X.; Wu, H.; Deng, J. Org. Chem. Front. 2022, 9, 6979.
- 7) (a) Mukai, K.; De Sant'Ana, D. P.; Hirooka, Y.; Mercado-Marin, E. V.; Stephens, D. E.; Kou, K. G. M.; Richter, S. C.; Kelley, N.; Sarpong, R. *Nature Chem* 2018, 10, 38. (b) Rovira, A. R.; Müller, N.; Deng, W.; Ndubaku, C.; Sarpong, R. *Chem. Sci.* 2019, 10, 7788. (c) Haley, H. M. S.; Payer, S. E.; Papidocha, S. M.; Clemens, S.; Nyenhuis, J.; Sarpong, R. J. Am. Chem. Soc. 2021, 143, 4732.
- (a) Haider, M.; Sennari, G.; Eggert, A.; Sarpong, R. J. Am. Chem. Soc.
 2021, 143, 2710. (b) Lusi, R. F.; Sennari, G.; Sarpong, R. Nat. Chem.
 2022, 14, 450. (c) Lusi, R. F.; Sennari, G.; Sarpong, R. J. Am. Chem.
 Soc. 2022, 144, 17277. (d) Sennari, G.; Gardner, K. E.; Wiesler, S.;
 Haider, M.; Eggert, A.; Sarpong, R. J. Am. Chem. Soc. 2022, 144, 19173.
- (a) Gershenzon, J.; Dudareva, N. Nat. Chem. Biol. 2007, 3, 408. (b) Rudolf, J. D.; Alsup, T. A.; Xu, B.; Li, Z. Nat. Prod. Rep. 2021, 38, 905.
- 10) Kanda, Y.; Ishihara, Y.; Wilde, N. C.; Baran, P. S. J. Org. Chem. 2020, 85, 10293.
- 11) Dickschat, J. S. Nat. Prod. Rep. 2016, 33, 87.
- 12) Ishihara, Y; Barab P. S. Synlett 2010, 12, 1733.
- 13) (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (b) Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P.

11

S. Science 2013, 341, 878. (c) Kawamura, S.; Chu, H.; Felding, J.; Baran, P. S. Nature 2016, 532, 90. (d) Chu, H.; Smith, J. M.; Felding, J.; Baran, P. S. ACS Cent. Sci. 2017, 3, 47. (e) Kuroda, Y.; Nicacio, K. J.; da Silva-Jr, I. A.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A. G.; Sette, L. D.; Williams, D. E.; Andersen, R. J.; Jancar, S.; Berlinck, R. G. S.; Sarpong, R. Nat. Chem. 2018, 10, 938. (f) Condakes, M. L.; Hung, K.; Harwood, S. J.; Maimone, T. J. J. Am. Chem. Soc. 2017, 139, 17783. (g) Wein, L. A.; Wurst, K.; Angyal, P.; Weisheit, L.; Magauer, T. J. Am. Chem. Soc. 2019, 141, 19589. (h) Berger, M.; Knittl-Frank, C.; Bauer, S.; Winter, G.; Maulide, N. Chem. 2020, 6, 1183.

- (a) Qiu, Y.; Gao, S. *Nat. Prod. Rep.* 2016, *33*, 562. (b) Abrams, D. J.;
 Provencher, P. A.; Sorensen, E. J. *Chem. Soc. Rev.* 2018, *47*, 8925. (c)
 Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. *Nat. Rev. Chem.* 2021, *5*, 522.
- 15) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. Acc. Chem. Res. **1995**, 28, 154.
- 16) (a) Corey, E. J.; Ohno, M.; Vatakencherry, P. A.; Mitra, R. B. J. Am. Chem. Soc. 1961, 83, 1251. (b) Corey, E. J.; Ohno, Masaji; Mitra, R. B.; Vatakencherry, P. A. J. Am. Chem. Soc. 1964, 86, 478.
- 17) Hoffmann, R. W. *Elements of Synthesis Planning*; Springer: 2009; pp 1–224.
- (18) Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. A J. Am. Chem. Soc. 1975, 97, 4777.
- (a) Marth, C. J.; Gallego, G. M.; Lee, J. C.; Lebold, T. P.; Kulyk, S.; Kou, K. G. M.; Qin, J.; Lilien, R.; Sarpong, R. *Nature* 2015, *528*, 493.
 (b) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* 2018, *140*, 8105. (c) Doering, N. A.; Sarpong, R.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* 2020, *59*, 10722.
- 20) Jiang, C.; Xue, J.; Yuan, Y.; Li, Y.; Zhao, C.; Jing, Q.; Zhang, X.; Yang, M.; Han, T.; Bai, J.; Li, Z.; Li, D.; Hua, H. *Phytochemistry* **2021**, *192*, 112939.
- 21) Fan, Y.-Y.; Xu, J.-B.; Liu, H.-C.; Gan, L.-S.; Ding, J.; Yue, J.-M. J. Nat. Prod. 2017, 80, 3159.
- 22) Ge, Z.-P.; Zhou, B.; Zimbres, F. M.; Cassera, M. B.; Zhao, J.-X.; Yue, J.-M. Chin. J. Chem. **2022**, 40, 1177.
- 23) (a) Xu, L.; Wang, C.; Gao, Z.; Zhao, Y.-M. J. Am. Chem. Soc. 2018, 140, 5653. (b) Zhang, H.; He, H.; Gao, S. Angew. Chem., Int. Ed. 2020, 59, 20417. (c) Zhang, H.; He, H.; Gao, S. Org. Chem. Front. 2021, 8, 555. (d) Lu, Y.; Xu, M.-M.; Zhang, Z.-M.; Zhang, J.; Cai, Q. Angew. Chem., Int. Ed. 2021, 60, 26610. (e) Li, A.; He, Z.; Liu, B.; Yang, Z.; Zhang, Z. Org. Lett. 2021, 23, 9237. (f) Qing, Z.; Mao, P.; Wang, T.; Zhai, H. J. Am. Chem. Soc. 2022, 144, 10640. (g) Sun, Z.; Fan, X.; Sun, Z.; Li, Z.; Niu, L.; Guo, H.; Ren, Z.; Wang, Y.; Hu, X. Org. Lett. 2022, 24, 7507. (h) Zhao, H.; Pan, H.; Yao, Y.; Huang, J.; Chen, Y. Synthesis 2022, 54, 3317.
- 24) Cai, Q. Chin. J. Chem. 2019, 37, 946.
- 25) Leonardi, G.; Truscello, A.; Mondrone, G. G.; Sebastiano, R. Results Chem. 2022, 4, 100280.
- 26) Molander, G. A.; Sandrock, D. L. Org. Lett. 2009, 11, 2369.
- 27) Huang, G.; Kouklovsky, C.; Torre, A. Chem. Eur. J. 2021, 27, 4760.
- 28) Stateman, L.; Nakafuku, K.; Nagib, D. Synthesis 2018, 50, 1569.
- 29) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Chem. Soc. Rev. 2015, 44, 7764.
- 30) Su, W.; Gong, T.; Lu, X.; Xu, M.; Yu, C.; Xu, Z.; Yu, H.; Xiao, B.; Fu, Y. Angew. Chem., Int. Ed. 2015, 54, 12957.
- 31) Clausen, F.; Kischkewitz, M.; Bergander, K.; Studer, A. Chem. Sci. 2019, 10, 6210.
- 32) (a) Miyai, T.; Ueba, M.; Baba, A. Synlett 1999, 1999, 182. (b) Yasuda,
 M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. J. Org. Chem. 2001, 66,
 7741.
- 33) Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. *Nature* 2013, 499, 192.
- 34) Gong, T.-J.; Xiao, B.; Cheng, W.-M.; Su, W.; Xu, J.; Liu, Z.-J.; Liu, L.; Fu, Y. J. Am. Chem. Soc. 2013, 135, 10630.
- 35) Li, Z.-Y.; Wang, G.-W. Org. Lett. 2015, 17, 4866.
- 36) Weitz, D. J.; Bednarski, M. D. J. Org. Chem. 1989, 54, 4957.
- 37) Mohite, A. R.; Phatake, R. S.; Dubey, P.; Agbaria, M.; Shames, A. I.; Lemcoff, N. G.; Reany, O. J. Org. Chem. 2020, 85, 12901.
- 38) Li, G.-X.; Morales-Rivera, C. A.; Gao, F.; Wang, Y.; He, G.; Liu, P.; Chen, G. *Chem. Sci.* **2017**, *8*, 7180.
- 39) Meystre, C. H.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. *Helv. Chim. Acta* 1962, 45, 1317.
- 40) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. J. Am. Chem. Soc. 2002, 124, 390. (b) Emmert, M. H.;

Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9409. (c) Miyazawa, K.; Ochi, R.; Koike, T.; Akita, M. *Org. Chem. Front.* **2018**, *5*, 1406. (d) Dragan, A.; Kubczyk, T. M.; Rowley, J. H.; Sproules, S.; Tomkinson, N. C. O. *Org. Lett.* **2015**, *17*, 2618. (e) Börgel, J.; Tanwar, L.; Berger, F.; Ritter, T. J. Am. Chem. Soc. **2018**, *140*, 16026.

- Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. Nature 2019, 567, 223.
- 42) (a) Ashley, J. N.; Hobbs, B. C.; Raistrick, H. Biochem. J. 1937, 31, 385. (b) Briggs, L. H.; Sutherland, M. D. J. Org. Chem. 1942, 7, 397. (c) Akiyoshi, S.; Erdtman, H.; Kubota, T. Tetrahedron 1960, 9, 237. (d) Barton, D. H. R.; Werstiuk, N. H. Chem. Commun. 1967, 30. (e) Barton, D. H. R.; Werstiuk, N. H. J. Chem. Soc. C 1968, 148. (f) Matsuo, A.; Nakayama, M.; Hayashi, S. Chem. Lett. 1973, 769.
- 43) (a) Welch, S. C.; Walters, R. L. Synth. Commun. 1973, 3, 419. (b) Welch, S. C.; Walters, R. L. J. Org. Chem. 1974, 39, 2665. (c) Kuo, D. L.; Money, T. J. Chem. Soc., Chem. Commun. 1986, 0, 1691. (d) Kuo, D. L.; Money, T. Can. J. Chem. 1988, 66, 1794. (e) Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. Org. Lett. 1999, 1, 391. (f) Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. J. Org. Chem. 2000, 65, 4112.
- 44) (a) McMurry, J. E.; Isser, S. J. J. Am. Chem. Soc. 1972, 94, 7132. (b) Oppolzer, W.; Godel, T. J. Am. Chem. Soc. 1978, 100, 2583. (c) Schultz, A. G.; Pulg, S. J. Org. Chem. 1985, 50, 915. (d) Lei, B.; Fallis, A. G. J. Am. Chem. Soc. 1990, 112, 4609. (e) Ho, T.-L.; Yeh, W.-L.; Yule, J.; Liu, H.-J. Can. J. Chem. 1992, 70, 1375.
- (a) Kasitu, G. C.; ApSimon, J. W.; Blackwell, B. A.; Fielder, D. A.; Greenhalgh, R.; Miller, J. D. *Can. J. Chem.* **1992**, *70*, 1308. (b) Alam, M.; Jones, E. B. G.; Hossain, M. B.; van der Helm, D. J. Nat. Prod. **1996**, *59*, 454. (c) Bahadoor, A.; Schneiderman, D.; Gemmill, L.; Bosnich, W.; Blackwell, B.; Melanson, J. E.; McRae, G.; Harris, L. J. J. Nat. Prod. **2016**, *79*, 81.
- 46) Masarwa, A.; Weber, M.; Sarpong, R. J. Am. Chem. Soc. 2015, 137, 6327.
- 47) Bermejo, F. A.; Fernández Mateos, A.; Marcos Escribano, A.; Martín Lago, R.; Mateos Burón, L.; Rodríguez López, M.; Rubio González, R. *Tetrahedron* 2006, 62, 8933.
- 48) Lo, J. C.; Yabe, Y.; Baran, P. S. J. Am. Chem. Soc. 2014, 136, 1304.
- (a) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. Angew. Chem. Int. Ed. 2011, 50, 6119. (b) Spinnato, D.; Schweitzer-Chaput, B.; Goti, G.; Ošeka, M.; Melchiorre, P. Angew. Chem. Int. Ed. 2020, 59, 9485.
- 50) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343.
- 51) Maddigan-Wyatt, J.; Hooper, J. F. Adv. Synth. Catal. 2021, 363, 924.
- 52) (a) Su, X.; Huang, H.; Yuan, Y.; Li, Y. Angew. Chem., Int. Ed. 2017,
- 56, 1338. (b) Liu, S.; Jie, J.; Yu, J.; Yang, X. Adv. Synth. Catal. 2018, 360, 267.
- 53) (a) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (b) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566.
- 54) (a) Curci, R.; D'Accolti, L.; Fusco, C. Acc. Chem. Res. 2006, 39, 1.
 (b) Zou, L.; Paton, R. S.; Eschenmoser, A.; Newhouse, T. R.; Baran, P. S.; Houk, K. N. J. Org. Chem. 2013, 78, 4037.
- 55) (a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Chem. Rev. 2017, 117, 8754. (b) Zhang, Q.; Shi, B.-F. Chem. Sci. 2021, 12, 841.
- 56) Mo, F.; Tabor, J. R.; Dong, G. Chem. Lett. 2014, 43, 264.
- 57) (a) Vermeulen, N. A.; Chen, M. S.; Christina White, M. *Tetrahedron* 2009, 65, 3078. (b) Gormisky, P. E.; White, M. C. J. Am. Chem. Soc. 2013, 135, 14052. (c) Zhao, J.; Nanjo, T.; de Lucca, E. C.; White, M. C. *Nature Chem.* 2019, 11, 213. (d) Chambers, R. K.; Zhao, J.; Delaney, C. P.; White, M. C. Adv. Synth. Catal. 2020, 362, 417.
- 58) Griffin, J. D.; Vogt, D. B.; Du Bois, J.; Sigman, M. S. ACS Catal. **2021**, *11*, 10479.
- 59) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. J. Am. Chem. Soc. 2004, 126, 9542. (b) Neufeldt, S. R.; Sanford, M. S. Org. Lett. 2010, 12, 532.
- 60) (a) Simmons, E. M.; Hartwig, J. F. *Nature* **012**, *483*, 70. (b) Karmel, C.; Li, B.; Hartwig, J. F. J. Am. Chem. Soc. **2018**, *140*, 1460.
- 61) (a) Tamao, K.; Ishida, N.; Kumada, M. J. Org. Chem. 1983, 48, 2120.
 (b) Fleming, I.; Henning, R.; Plaut, H. J. Chem. Soc., Chem. Commun. 1984, 29.
- 62) Isayama, S.; Mukaiyama, T. Chem. Lett. 1989, 18, 1071.
- 63) Siler, D. A.; Mighion, J. D.; Sorensen, E. J. Angew. Chem. Int. Ed. 2014, 53, 5332.
- 64) Caglioti, L.; Magi, M. Tetrahedron 1963, 19, 1127.