Published in final edited form as:

Tetrahedron. 2016 November 10; 72(45): 7093–7123. doi:10.1016/j.tet.2016.08.053.

Metallacycle-Mediated Cross-Coupling in Natural Product Synthesis

Natasha F. O'Rourke[†], Matthew J. Kier[†], and Glenn C. Micalizio

Burke Laboratory, Department of Chemistry, Dartmouth College, Hanover, NH 03755, United States

Graphical abstract

Keywords

Metallacycle-mediated cross-coupling; Convergent C–C bond formation; [2+2+1]; [2+2+2]; Catalyzed Alder-ene; Natural product synthesis

1. Introduction

Reaction processes that forge carbon–carbon bonds in a highly selective fashion sculpt the landscape of organic chemistry and play a profound role in natural product synthesis. In turn, it is well appreciated that total synthesis defines a stringent test for reaction methods and serves as a measure of their power to affect chemo- and stereoselective transformations in complex and diverse settings.¹ As eloquently noted by Professor K. C. Nicolaou, “ever since the first laboratory construction of a carbon–carbon bond by Kolbe in his historic synthesis of acetic acid in 1845, carbon–carbon bond-forming reactions have played an enormously decisive and important role in shaping chemical synthesis.”² In fact, new C–C bond-forming processes that offer unique retrosynthetic relationships can have a profound

[†]These authors contributed equally.

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impact on the future of chemical synthesis, as well as neighboring disciplines where organic molecules play an important, if not central, role. While classic examples of powerful C–C bond-forming processes include aldol- and Grignard-type reactions, cycloadditions, sigmatropic rearrangements and other pericyclic processes, cation-olefin and radical cyclizations, modern advances have witnessed the emergence of metal-catalyzed cycloisomerization, cross-coupling (*e.g.*, Pd- and Ni-), and olefin/alkyne metathesis.

Unique among these diverse classes of chemical reactivity are those that can be effectively employed in intermolecular settings, hence providing opportunities for convergent coupling. Convergency is among the most important strategic considerations in complex molecule synthesis, as it provides a means to decrease the longest linear sequence of chemical transformations required to convert simple starting materials into complex structures.³ Because yields of organic reactions are typically less than quantitative, significant contraction in the length of such sequences used to prepare a target can have a profound impact on efficiency. Of additional value, points of convergency in a synthesis pathway offer opportunities to introduce structural variation in a straightforward fashion – a feature of relevance in medicinal pursuits.⁴ It is instructive to recognize that most classical methods for convergent coupling by C–C bond formation are based on nucleophilic addition to polarized π -bonds (aldol and Grignard-type chemistry, carbonyl olefination, and 1,4-addition) and cycloaddition reactions. Modern advances have introduced distinct strategies for coupling that afford complementary bond constructions to these classic methods.^{1, 2} Such processes have had a profound impact on organic synthesis, with Pd-catalyzed cross-coupling and olefin metathesis each being recognized with a Nobel Prize.

In this review we place emphasis on an emerging collection of intermolecular C–C bond-forming processes that offer distinct retrosynthetic relationships in comparison to the now well-established strategies discussed above. The collection of reactions of interest here can be broadly characterized as metallacycle-mediated cross-coupling, and our focus is to cover those processes that have been demonstrated to be useful in natural product total synthesis.

At the outset of this discussion we recognize that a great variety of organic reactions are thought to proceed by way of metallacyclic intermediates, perhaps among the most popular of which are metathesis reactions (Figure 1A). These processes have had a transformative impact on organic synthesis, with their power often being wielded in intramolecular ring-forming chemistry (reactions that, by definition, are not convergent – rather, they are unimolecular). The development of versions of metathesis chemistry that allow for effective and stereoselective cross-coupling, and the application of such techniques to achieve convergent coupling in natural product synthesis, is certainly of great current interest, but such chemistry has been reviewed elsewhere.¹

Here, we focus on a related and diverse collection of metallacycle-mediated coupling reactions that are thought to proceed through distinct metallacyclic intermediates – metallacyclopentanes (and analogs thereof) rather than metallacyclobutanes (Figure 1B). A large variety of coupling partners have been demonstrated to be compatible with this class of reactivity and, in some cases, many different stereoselective methods are available for each. In many instances the final organometallic intermediates generated in the course of these

cross-coupling reactions can be functionalized in a number of different ways to establish a variety of diverse retrosynthetic relationships that derive from a common class of chemical reactivity.

From a historical perspective, this class of coupling chemistry was described nearly 70 years ago with the trimerization of acetylene as an approach to the formation of benzene (the Reppe reaction).⁵ Nearly thirty years after this discovery, the first demonstrations of powerful metallacycle-mediated cross-coupling chemistry began to appear in the context of natural product synthesis – Vollhardt's use of Co-mediated [2+2+2] chemistry for the synthesis of estrone in 1980.⁶ While the latter part of the 20th century was marked by spectacular contributions at the interface of organometallic and synthetic organic chemistry, the last two decades have witnessed a substantial increase in contributions that feature the development of metallacycle-mediated cross-coupling chemistry and application of these processes in natural product synthesis.

We have organized this report in a manner that is primarily focused on the nature of the coupling partners employed in the key metallacycle-mediated cross-coupling step (*i.e.*, alkyne–alkyne, alkyne–alkene, alkene–imine, *etc.*). Attention will be paid to chronology within each subset of coupling processes discussed, but the overall presentation will follow a sequence that we believe is appropriate from a pedagogical standpoint. In some cases we offer a brief discussion of the proposed mechanism and origin of selectivity associated with the metallacycle-mediated coupling process of relevance.

Overall, we hope that this Report serves to unify a class of eclectic, yet powerful, C–C bond-forming reactions as belonging to a broader, single class of chemical reactivity: “metallacycle-mediated cross-coupling.” Our focus on discussing applications in natural product synthesis is meant to demonstrate the great power that these reactions have in complex and diverse molecular settings, while providing a collection of examples that serve to educate the reader as to where such reactions have been employed in the context of larger molecular challenges.

2. General Considerations

In planning to use any metallacycle-mediated cross-coupling reaction in natural product synthesis, one must be familiar with general considerations associated with this class of reactivity. The first of these is simple reactivity. While many examples of metallacycle-mediated C–C bond formation have appeared in the context of intramolecular chemistry, achieving success in intermolecular settings is substantially more challenging (Figure 2A). In fact, there are many intramolecular bond-forming processes in this class that are extremely challenging to accomplish in an intermolecular fashion (*i.e.*, alkene–alkene and alkyne–alkene). Once confidence is gained for being able to achieve desired levels of reactivity, one must pay attention to regioselection (Figure 2B). With unsymmetrically substituted π -systems, as one would anticipate encountering in most natural product synthesis settings, the most useful reactions in this class must proceed with site-selectivity (*i.e.*, which carbon of each unsymmetrical π -system gains a C–C bond). Next, depending on the nature of the coupling partners employed, one may need to consider diastereoselectivity

(Figure 2C) and enantioselectivity. Finally, with a plan to employ metallacycle-mediated cross-coupling reactions in complex settings, one must also consider chemoselectivity and functional group compatibility. As will be evident in the various sections of this review, great advances have been made that address these considerations, revealing coupling reactions that are quite useful in highly complex settings.

3. Alkyne–Alkyne Cross-Coupling

Introduction

Alkynes have played a prominent role in the development of metallacycle-mediated cross-coupling chemistry. The earliest reports embraced homo-trimerization⁵ and homo-dimerization⁷ *en route* to benzene and metallacyclopentadienes of Group IV metals. Subsequent achievements by Professors Buchwald, Negishi and Takahashi in the late 1980's and mid-1990's led to the realization of methods to cross-couple alkynes through processes that delivered Cp₂Zr-based metallacyclopentadienes.^{8–12}

In 1999 a significant departure from Group IV metal–Cp₂ complexes appeared and paved a new path for the development of metallacycle-mediated alkyne–alkyne cross-coupling chemistry. From a program aimed at exploring the reactivity of an organometallic intermediate generated from the combination of Ti(O*i*-Pr)₄ and 2RMgX (conditions previously explored for the Kulinkovich reaction^{13, 14}), Professor Sato described a simple process for the regioselective coupling of internal alkynes with terminal alkynes (Figure 3A).¹⁵ Regioselectivity in this process was controlled using a sterically or electronically biased internal alkyne as the first coupling partner (TMS-substituted or highly polarized, respectively) and a terminal alkyne as the second coupling partner. As such, highly selective versions of this process required forming 1,3-dienes that possess these groups at the 1-position.

In efforts aimed at establishing metallacycle-mediated cross-coupling chemistry that could address 1,3-diene motifs that are encountered in a wide range of polyketide-derived targets, the Micalizio laboratory investigated the coupling reactions summarized in Figure 3B.¹⁶ Their studies ultimately led to the conclusion that a distal hydroxyl group imparts a substantial bias to control regioselectivity of the process, independent of the relative stereochemistry of the internal alkyne coupling partner (eq. 1). These studies also revealed a moderate directing effect of homopropargylic alcohols (eq. 2) and described the inherent regioselectivity of coupling reactions of internal alkyne substrates that lack a free hydroxyl directing group (eq. 3). In these latter two classes of coupling reactions (eqs. 2 and 3), relative stereochemistry of the internal alkyne coupling partner was found to also impact regioselectivity of the process.^{16, 17} Despite the variable nature of regioselectivity observed, this type of coupling process has been employed in a variety of natural product settings, *vide infra*.

A. Total Synthesis of Callystatin A

In 2008, the first use of a metallacycle-mediated alkyne–alkyne cross-coupling reaction in natural product synthesis was published.¹⁸ This demonstration appeared in efforts targeting

the total synthesis of callystatin A (Figure 4A), a rare and highly cytotoxic member of the leptomycin class of natural products.¹⁹ The Micalizio laboratory reported a highly convergent synthesis that proceeded by way of a coupling reaction that forged the C13–C14 bond and established the accompanying (*E,E*)-1,3-diene motif. Their study was complemented by concise 7- and 6-step syntheses of coupling partners **1** and **2** and highlighted the use of a Ti-mediated alkyne–alkyne coupling to generate the functionalized late-stage intermediate **3** (76% yield, *rr* = 5:1; Figure 4B). The success of this coupling reaction is notable, as it demonstrated chemoselectivity for engaging the terminal alkyne of polyunsaturated substrate **2**, while also showing compatibility with a dienyl ether and allylic acetal.

Finally, it is worth pointing out that this bond construction delivers a stereodefined 1,3-diene in an efficient, convergent manner without requiring stereodefined olefinic coupling partners – motifs that are typically required for Pd-catalyzed cross-coupling chemistry.

B. Formal Total Synthesis of Dictyostatin

Dictyostatin is a rare macrolide from marine origin (most recently isolated from the Caribbean sponge *Corallistidae* sp.) that exhibits potent anticancer properties (Figure 5A).²⁰ Related to the marine natural product discodermolide, this agent retains activity against multi-drug resistant cell lines. With the withdrawal of discodermolide from clinical trials in 2005, significant interest has been directed toward dictyostatin, particularly since the natural supply is vanishingly scarce. These considerations and the potential to develop new applications of metallacycle-mediated cross-coupling chemistry led the Micalizio group to pursue its synthesis.²¹

In contrast to their use of alkyne–alkyne coupling to address the central 1,3-diene of callystatin A, previously discussed, here they opted to explore the use of this type of cross-coupling chemistry to establish the stereodefined northern hemisphere of the target – a structure that lacks a 1,3-diene. As illustrated in Figure 5A, they set their sights on the C16–C17 bond and relied on subsequent stereoselective hydrogenation to generate the requisite stereochemistry at C16. As summarized in Figure 5B, Ti-mediated coupling of the internal alkyne **4** with terminal alkyne **5** proceeded well and, after selective desilylation, delivered the 1,3-diene-containing product **6** in 63% yield (*rr* = 20:1). Subsequent use of a stereoselective hydrogenation then delivered fragment **8**. Seven additional steps were employed to advance this species to an intermediate that Paterson converted to dictyostatin through nine subsequent chemical transformations.²²

C. Total Synthesis of Virginiamycin M₂

The virginiamycins are a class of antibiotics produced by *Streptomyces* that have been used as dietary supplements to accelerate the growth of animals and to prevent and treat bacterial infections. Natural and synthetic derivatives of the virginiamycins have been found to possess potent antibiotic activity against methicillin-, erythromycin-, and vancomycin-resistant *S. aureus*.²³ In 2010, Panek reported a total synthesis of virginiamycin M₂ employing a metallacycle-mediated cross-coupling as a key step (Figure 6A).^{24, 25} With a bold plan in mind, Panek and coworkers targeted the establishment of the C8–C9 bond by

Ti-mediated union of the propargylic alcohol **9** with terminal alkyne **10** (Figure 6B). Notably, both coupling partners possessed unprotected hydroxyl- groups, and the terminal alkyne component also contained an α,β -unsaturated secondary amide. Demonstrating the functional group compatibility of this class of metallacycle-mediated cross-coupling, they reported a Ti-mediated reaction process that delivered triene **11** in 58% yield, and with outstanding levels of regioselectivity.

D. Total Synthesis of the Proposed Structure of Heronamide C

Heronamide C is a member of a large class polyene macrocyclic lactam-containing natural products produced from *Streptomyces* sp. that has been reported to have a pronounced and unique effect on the morphology of cultured cells.²⁶ Pursuing their interest in the chemistry and biology of polyene macrolactams, the Kanoh laboratory at Tohoku University targeted the total synthesis of the proposed structure of heronamide C (Figure 7A).²⁷ In 2014, the authors reported the Ti-mediated coupling of propargylic ether **12** with conjugated enyne **13** – a process that delivered the stereodefined conjugated triene **14** in 64% yield and that proceeded with good levels of regioselectivity (rr = 12:1). Notably, their success with this coupling reaction highlighted the ability to avoid elimination chemistry possible with both the intermediate Ti-complex of **12** (see Figure 7C), and the metallacyclopentadiene formed upon alkyne–alkyne coupling.²⁸

E. Synthesis and Discovery of Valerjesomycin

While not a natural product, Micalizio's function-oriented synthesis efforts in the area of benzoquinone ansamycins embraced the application of a metallacycle-mediated alkyne–alkyne coupling as a key convergent step. This chemistry fueled an SAR study that ultimately led to the discovery of valerjesomycin (Figure 8A) as a benzoquinone ansamycin-inspired agent with exquisite paralog selectivity for Hsp90 α and Hsp90 β over Grp94.²⁹ As illustrated in Figure 8B, these investigations targeted the construction of the C7–C8 bond by metallacycle-mediated cross-coupling between **15** and **16**. After hydrolysis of the ester, this sequence delivered seco-acid **17** in 52% yield as an 8:1 mixture of regioisomers. Their success in this process demonstrated the ability to generate a Ti–alkyne complex on a substrate that contains a free aniline (**15**) and revealed chemoselectivity for reaction of the Ti-alkyne complex of **15** with the terminal alkyne of **16** in preference to the α,β -unsaturated ethyl ester.

4. Alkene–Alkyne Cross-Coupling

Introduction

In early investigations of the potential utility of metallacycle-mediated bond-formation in organic synthesis, intramolecular reactions took center stage. It was here where the first examples of alkene–alkyne coupling processes emerged in the context of forming carbo- and heterocyclic systems.^{30–33} While adopted by the synthetic organic chemistry community in short order, these processes remained limited to intramolecular settings – for the generation of 5- and 6-membered rings (Figure 9A). The challenge of accomplishing alkene–alkyne cross-coupling (intermolecular) is related to the low reactivity of substituted alkenes in the intermolecular carbometalation step and the established instability of the

metallacyclopentene intermediates that result from cross-coupling.^{34, 35} As illustrated in Figure 9B, a central feature of Negishi's alkyne–alkyne coupling process took advantage of this instability. Treatment of an alkyne with the organometallic species generated from addition of 2 equiv. of EtMgBr to Cp₂ZrCl₂ generates a zirconacyclopentene intermediate. This species serves as an effective source of a Zr-alkyne complex (with loss of ethylene) that can participate in coupling with a variety of different π -systems (*e.g.*, alkynes, nitriles, aldehydes).³¹

Despite the instability of metallacyclopentene intermediates, methods have become available for the regio- and stereoselective metallacycle-mediated cross-coupling of alkenes with alkynes. An early example, that has had a significant impact in natural product synthesis, is Trost's Ru-catalyzed Alder-ene reaction (Figure 10).^{36, 37} Here, metallacycle-formation is followed by trapping of the unstable organometallic intermediate by regio- and stereoselective β -hydride elimination and reductive elimination – a sequence that results in a 1,4-diene-containing product and regenerates the active catalyst.

Recently, Group IV metal-mediated coupling chemistry has emerged as an alternative approach to alkene–alkyne coupling that affords complementary bond-constructions to the Ru-catalyzed Alder-ene reaction. The first of these was offered by Professor Takahashi and proceeded through a pathway that trapped the metallacyclopentene intermediate by elimination (Figure 11A).^{38–40} While effective, this approach afforded products as mixtures of alkene stereoisomers – an undesirable trait that has likely resulted in a lack of adoption of this reaction in natural product synthesis. In a departure from the use of Cp₂M-based species, and in the context of studies aiming to render the metallacycle-mediated cross-coupling alkoxide-directed, Micalizio and Cha described highly stereoselective alkyne–allylic alcohol coupling processes that established (*E*)-disubstituted or (*Z*)-trisubstituted alkenes (Figure 11B).^{41, 42} Here, reversible docking of the alkene substrate to the preformed metallacyclopentene by Ti–O bond formation is proposed to result in an opportunity for intramolecular carbometallation through a boat-like transition state. Minimization of allylic strain (1,3- or 1,2-) was then rationalized as the means by which one can attain high levels of stereocontrol for the formation of 1,4-dienes containing either an (*E*)-disubstituted or (*Z*)-trisubstituted alkene.

The Ru-catalyzed Alder-ene reaction and alkoxide-directed Ti-mediated alkyne–allylic alcohol coupling have been used in a variety of natural product syntheses.

A. Total Synthesis of Acetogenins

The first examples that revealed the great power of Ru-catalyzed Alder-ene reactions in total synthesis were focused on the assembly of members of the acetogenin family of natural products. The version of this reaction that was central to these campaigns involved the coupling of alkynoates to terminal alkenes. As illustrated in Figure 12A, the relevant metallacycle-mediated alkyne–alkene coupling reaction is thought to proceed by regioselective formation of a ruthenium-based metallacyclopentene that, after β -hydride elimination and reductive elimination, unveils a species that promptly cyclizes to generate a γ -lactone.⁴³ Regioselectivity with respect to the alkyne reaction partner has been proposed to derive from preferential coordination of the alcohol to the metal center.

Two examples where this variant of the Alder-ene reaction has been particularly effective are in the total syntheses of acetogenins (+)-ancepsenolide and (+)-solamin, highlighted in Figure 12B and Figure 12C, respectively. In studies directed toward the total synthesis of ancepsenolide, Trost demonstrated the ability to employ a Ru-catalyzed Alder-ene reaction in a two-directional fashion (Figure 12B).⁴⁴ Union of **18** with **19** delivered tetraene **20** in 75% yield, and this species was converted to the natural product by chemoselective reduction of the electron rich disubstituted alkenes. In a similar manner, solamin was prepared by a related Alder-ene reaction of **18** with **21** (Figure 12C).⁴⁵ Here, the key metallacycle-mediated coupling process was demonstrated to be chemoselective, engaging only the terminal alkene of **21** in the C–C bond-forming event. Overall, these examples highlight the utility of Ru-catalyzed Alder-ene reaction for the installation of γ -lactones in complex settings.⁴⁶

B. Total Synthesis of the Proposed Structure of Trocheliophorolide B

In 2012, an interesting application of the Ru-catalyzed Alder-ene reaction appeared in the context of Trost's studies directed toward synthesis of the proposed structure of trocheliophorolide B (Figure 13A).⁴⁷ As illustrated in Figure 13B, a γ -lactone-forming process was executed between alkyne **18** and allyl alcohol (**23**). Here, the Alder-ene process delivered an enol after β -hydride elimination – a product that then isomerized to an aldehyde. This version of metallacycle-mediated alkyne–alkene coupling led to the synthesis of the proposed structure of trocheliophorolide B in just three addition steps.

C. Total Synthesis of Deschlorocallipeltoside A

Callipeltoside A is a cytotoxic marine-derived polyketide that inhibits *in vitro* proliferation of NSCLC-N6 human bronchopulmonary non-small-cell lung carcinoma and P388 cells (Figure 14A).⁴⁸ In a program aimed at defining a synthetic means to access this natural product and synthetic analogs with potential medicinal value, Trost described the application of Ru-catalyzed alkene–alkyne coupling to establish the C11–C12 bond in a sequence that first led to the production of deschlorocallipeltoside A.⁴⁹ This alkyne–alkene coupling is notably different than that previously employed by Trost for γ -lactone synthesis in that the alkyne was not significantly polarized. As illustrated in Figure 14B, coupling of alkyne **25** with the protected homoallylic alcohol **26** generated the 1,4-diene product **27** in 85% yield. Regioselectivity in this case was proposed to be influenced by the ability of the propargylic methyl ether to co-ordinate to ruthenium in the intermediate metallacyclopentene. Notably, Trost's efforts directed toward the synthesis of deschlorocallipeltoside A paved the way for his group's success in achieving a total synthesis of callipeltoside A – an achievement that resulted in the correct assignment of the absolute and relative stereochemistry of this potent marine-derived toxin.^{50, 51}

D. Formal Total Synthesis of Alternaric Acid

Alternaric acid is a polyunsaturated and stereochemically rich natural product that was first isolated in 1949 from *Alternaria solani* (Figure 15A).⁵² Aside from its interesting structure, this compound was found to possess highly selective activity for inhibiting germination of certain fungal strains as well as demonstrating activity as a selective phytotoxic agent.⁵³

Trost reported a total synthesis of this agent via application of his Ru-catalyzed alkyne–alkene coupling method, here through regioselective coupling of a terminal alkene (**28**) with a terminal alkyne (**29**; Figure 15B).⁵⁴ This coupling process proceeded in 65% yield and delivered the 1,4-diene product **30** with 13:1 regioselectivity.

E. Formal Total Synthesis of Mycalamide A

Mycalamide A is a marine sponge-derived natural product that possesses potent antiviral and antitumor properties as a result of its ability to arrest protein synthesis (Figure 16A).⁵⁵ Trost and coworkers accomplished a formal total synthesis of this agent that focused on preparation of the pederic acid unit via construction of the C4–C5 bond.⁵⁶ As illustrated in Figure 16B, Ru-catalyzed alkyne–alkene coupling between **31** and **32** proceeded in a regioselective fashion, with C–C bond formation occurring distal to the TMS group of the alkyne. The Alder-ene process delivered, as anticipated, the (*E*)- α,β -unsaturated ester-containing diene product **33**.

F. Total Synthesis of Amphidinolides A and P

The amphidinolides are a family of structurally diverse cytotoxic natural products from symbiotic dinoflagellates of the genus *Amphidinium*.⁵⁷ Members of this class have served to inspire a variety of campaigns in total synthesis, two of which marked the exploration of Ru-catalyzed alkyne–alkene coupling. In Trost's synthesis of amphidinolide A (Figure 17A), an effort that led to the structure elucidation of the natural product, two impressive applications of metallacycle-mediated C–C bond formation were explored: (1) alkyne–alkene cross-coupling to forge the C6–C7 bond, and (2) macrocyclization by a Ru-mediated Alder-ene reaction.^{58–60} The metallacycle-mediated cross-coupling that was successful in these campaigns is illustrated in Figure 17B. In this remarkable process, the polyunsaturated alkyne **34** was effectively coupled to the 1,4-diene **35**. While the product **36** was isolated in only 23% yield, this example supports the great chemoselectivity associated with Ru-catalyzed coupling processes and demonstrates that polymerization of **34** can be avoided (it contains both functionality required for Alder-ene chemistry – the reactive alkyne and the terminal alkene).

Amphidinolide P also proved a worthy target for the Trost group (Figure 18).^{61, 62} Here, they targeted alkene–alkyne coupling technology for the establishment of the C10–C11 bond. As illustrated in Figure 18B, success was seen in the union of β -lactone containing enyne **37** with terminal alkyne **38** – a process that delivered **39** in 75% yield with high levels of selectivity. The observed regioselectivity with respect to the alkyne is likely attributed to non-bonded steric interactions between the substituent on the terminal alkyne and the ligands on ruthenium during formation of the metallacyclopentene intermediate.

G. Total Synthesis of (–)-Dactylolide

Dactylolide is a natural product that has attracted a significant amount of attention as a target for total synthesis, not only because of its unique structure – it selectively inhibits the growth of a subset of human tumor cell lines (Figure 19A).⁶³ Lee's synthesis of (–)-dactylolide focused on the use of a variety of metal-catalyzed transformations, not the least of which included two Ru-catalyzed alkene–alkyne coupling reactions to forge the C5–C6 and the

C13–C14 bonds.⁶⁴ The former of these was accomplished through a pathway that likely does not involve the intermediacy of a metallacyclopentene. The latter, however, embraces the Ru-catalyzed Alder-ene process. As illustrated in Figure 19B, coupling of the protected homoallylic alcohol **40** with the homopropargylic alcohol **41** generated the 1,4-diene-containing product **42** – a compound that was suitably functionalized for a Pd-catalyzed etherification reaction *en route* to the stereodefined 2,6-*cis*-disubstituted pyran **43**.

H. Total Synthesis of Bryostatin 16

The bryostatins are a collection of rare, marine-derived macrocyclic lactones that have attracted substantial interest from members of the scientific community. They were originally isolated from the marine bryozoan *Bugula neritina* and were found to exhibit exceptional biological activity, most notably their anticancer activity *in vivo*.⁶⁵ Perhaps not surprisingly, some of the world's leaders in organic chemistry have spent substantial energy devising strategies to prepare members of this class.

In Trost's impressive contribution, he set his sights on bryostatin 16 (Figure 20A).^{66, 67} Here, a highly convergent metallacycle-mediated alkyne–alkene coupling process was explored for construction of the C12–C13 bond. As illustrated in Figure 20B, union of the β,γ -unsaturated ketone **44** with the TMS-alkyne **45** proceeded to deliver the metastable intermediate **46**, which was suitably functionalized to undergo stereoselective intramolecular 1,4-addition. Overall, the coupling process led to the generation of a substantial substructure of the natural product target (**47**) in 34% yield.

I. Total Synthesis of Lehualide B

The lehualides are a family of pyrone-containing marine-derived natural products that were originally described as having moderate and selective cytotoxicity *in vitro* (IGROV-ET and K562 cell lines).⁶⁸ The skipped polyunsaturated nature of lehualide B (Figure 21A) attracted the attention of the Micalizio laboratory, posing what appeared to be a suitable target for application of a recently developed alkoxide-directed titanium-mediated allylic alcohol–alkyne coupling reaction.⁶⁹ Their synthesis strategy explored the use of such a metallacycle-mediated coupling to establish the C14–C15 bond in concert with setting the stereochemistry of the two trisubstituted olefins of the local 1,4-diene motif. As illustrated in Figure 21B, the polyunsaturated pyrone-containing allylic alcohol **48** was coupled to the TMS-alkyne **49** to deliver the stereodefined product **50** in 61% yield, with 20:1 regioselectivity and 7:1 selectivity in favor of the desired *Z*-trisubstituted alkene. These efforts resulted in the first total synthesis of lehualide B and the discovery that this agent has impressive and highly selective activity against multiple myeloma cell lines (EC_{50} = 2.9 nM and 2.1 nM in U266 and RPMI 8226 cells, respectively). While not depicted in Figure 21, the Micalizio group executed a function-oriented synthesis study targeting synthetic analogues of lehualide B – a program that explored a number of variants of the allylic alcohol–alkyne coupling process and produced numerous natural product analogs with potent and selective cytotoxicity toward multiple myeloma cell lines.⁷⁰

J. Total Synthesis of (–)-Vittatalactone

In efforts to explore the use of Ti-mediated allylic alcohol–alkyne coupling chemistry for the convergent synthesis of deoxypropionates, the Micalizio laboratory pursued the synthesis of (–)-vittatalactone (Figure 22A) – a deoxypropionate natural product that was isolated in a search for sex pheromones specific to the cucumber beetle *Acylymma vittatum* (an insect that causes major damage to the cucurbit crops in North America).⁷¹ Their efforts focused on establishment of the C6–C7 bond and featured the metallacycle-mediated cross-coupling depicted in Figure 22B. Union of alkyne **51** and allylic alcohol **52**, followed by desilylation, resulted in the formation of 1,4-diene **53** in 63% yield. The central metallacycle-mediated coupling process proceeded with exquisite regio- and stereocontrol, delivering a single 1,4-diene product. Conversion of diene **53** to the deoxypropionate motif central to the vittatalactone structure (**54**) was then affected by simple hydroxyl-directed hydrogenation.

K. Total Synthesis of Phorbasin C

The phorbasins are a class of structurally unique diterpenes that have been isolated from a southern Australian marine sponge (*Phorbas* sp.).^{72–76} Members of this class have been reported to possess a range of antibiotic and cytotoxic properties, with phorbasin C attracting the attention of the Micalizio laboratory (Figure 23A). While the structure of the target was not clear from the reported isolation, the Micalizio laboratory began a synthesis campaign that targeted the development of a regio- and stereoselective allylic alcohol–alkyne coupling process for establishment of the C6–C7 bond.⁷⁷ As illustrated in Figure 23B, this pursuit led to the successful metallacycle-mediated coupling of cyclohexene **56** to TMS-alkyne **49**. Here, alkoxide-directed Ti-mediated coupling proceeded with exquisite regio- and stereochemical control, delivering the 1,4-diene-containing product **57** as a single isomer in 47% yield.

While demonstrating the ability to achieve stereoselectivity in the formation of the C6 stereocenter, their success with this metallacycle-mediated coupling reaction also revealed the significant influence of non-bonded steric interactions in affecting the rate of C–C bond formation. No product was seen where a second equivalent of the Ti–alkyne complex engaged the allylic alcohol of **57** in a second C–C bond-forming process. Given the requirement for hydroxyl direction in this class of coupling reactions (low levels of reactivity are encountered with substrates that lack a directing group), this second coupling process would require C–C bond-formation from the same face of the alkene as the C6 substituent. Apparently, the steric impediment imposed by this group was sufficient to dissuade a second coupling process.

5. Alkyne–Aldehyde Cross-Coupling

Introduction

Unlike metallacycle-mediated coupling chemistry between alkenes and alkynes, where substantial barriers to achieving suitable reactivity are further complicated by challenges associated with controlling regioselectivity with respect to both reactive π -systems, reductive coupling processes between alkynes and aldehydes are relatively straightforward. In this subset of metallacycle-mediated cross-coupling reactions, reactivity is not a

substantial issue, leaving one only to deal with addressing regioselectivity with only one π -component (the alkyne; Figure 24), and stereoselectivity associated with the allylic alcohol product. While a variety of methods are available to accomplish alkyne–aldehyde reductive cross-coupling in a highly selective fashion (regio- and stereo-),^{78–100} a relatively small subset of these reaction processes have been successfully employed in natural product synthesis. The following examples are illustrative.

A. Total Synthesis of (–)-Terpestacin

Terpestacin, a structurally complex sesterterpene natural product that selectively inhibits angiogenesis, has risen as an attractive target for total synthesis (Figure 25A).^{101–107} In 2003, Jamison reported an enantioselective synthesis of this natural product that featured two different metallacycle-mediated coupling reactions: (1) an early example of metallacycle-mediated alkyne–aldehyde coupling in natural product synthesis, and (2) an intermolecular Pauson–Khand annulation (a special type of metallacycle-mediated alkyne–alkene coupling that will be discussed later in this Report).^{108, 109} As illustrated in Figure 25B, Ni-catalyzed coupling of alkyne **58** to aldehyde **59** delivered the desired product **60** in 41% isolated yield, yet proceeded with only moderate levels of selectivity (*rs* = 2.6:1, *ds* = 2:1).

B. Total Synthesis of Macbecin I

The benzoquinone ansamycins are stereochemically complex macrocyclic lactams that have surfaced as attractive targets for synthesis due not only to their structures but also because of their properties as Hsp90 inhibitors. Shortly after studying the factors that influence regioselectivity in Ti-mediated alkyne–aldehyde coupling reactions, Micalizio reported a step-economical synthesis of one of the most active members of this class, macbecin I (Figure 26A).¹¹⁰ The targeted metallacycle-mediated alkyne–aldehyde coupling aimed to forge the C7–C8 bond and realize the highly convergent process depicted in Figure 26B. Preformation of a Ti-alkyne complex of **62** was followed by addition of the highly unstable polyunsaturated aldehyde **63**. After protonation of the intermediate oxametallacyclopentene, a mixture of regio- and stereoisomeric products was advanced through a saponification and macrolactamization process to afford the macrocyclic lactam **64** in 44% yield. While the authors could not assess the product mixture formed from the first step in this sequence (the alkyne–aldehyde coupling), they did report a related coupling reaction with a more stable aldehyde where they observed 7:1 regioselectivity and 3:1 diastereoselectivity. Overall, the successful application of metallacycle-mediated alkyne–aldehyde cross-coupling in the context of this synthesis of macbecin I shed light on the functional group compatibility and chemoselectivity of the process, revealing the ability to (1) form a Ti-alkyne complex in the presence of an unprotected aniline, and (2) selectivity in addition to an aldehyde in the presence of a dienyl ester.

C. Total Synthesis of D-Erythro-Sphingosine

In studies that originated from their interest in expanding the scope and utility of regio- and stereoselective Ni-catalyzed alkyne–aldehyde coupling reactions, Montgomery and coworkers demonstrated the use of this process in the total synthesis of D-erythro-

sphingosine (Figure 27A).¹¹¹ Here, the authors employed their *N*-heterocyclic carbene-modified Ni-catalyzed process to couple Garner aldehyde **65** to TMS-alkyne **66** (Figure 27B). Overall, they achieved C3–C4 bond-formation with exquisite levels of regio- and stereocontrol *en route* to **67**. Only two additional steps were required to complete the total synthesis.

D. Total Synthesis of Bryostatin 7

As previously discussed in the section of this Report covering Trost's synthesis of bryostatin 16, the bryostatins have attracted a substantial amount of attention from many members of the scientific community due to their profound biological properties, interesting structures, and low natural abundance. Bryostatin 7 captured the attention of the Krische group and served as a target that provided an opportunity for them to explore the application of a number of catalytic transformations that have been developed in their laboratory (Figure 28A).¹¹² Notably, their synthesis strategy targeted generation of the C20–C21 bond by a metallacycle-mediated alkyne–aldehyde cross-coupling reaction. As illustrated in Figure 28B, they employed a Rh-catalyzed metallacycle-mediated cross-coupling reaction between the highly electron deficient aldehyde **68** and enyne **69**, and realized a process that forged the C20–C21 bond and established the C20 stereocenter (*dr* = 7:1), producing allylic alcohol **62** in 77% yield.

E. Total Synthesis of Trienomycin A

Ansatrienins are a subset of “ansamycins” – polyketide-derived natural products that are known to possess an important portfolio of antibiotic properties. Trienomycins are members of the ansatrienin class that have antineoplastic activity.^{113–115} Trienomycins A and F were selected by Krische and coworkers as targets for synthesis, where the C3–C4 bond was selected for establishment by application of their unique Ru-catalyzed acetylene–aldehyde coupling reaction (Figure 29A).¹¹⁶ As depicted in Figure 29B, metallacycle-mediated coupling of aldehyde **72** with acetylene resulted in stereoselective synthesis of the dienylic alcohol **73** in 83% yield (85% ee, *Z:E* = 20:1). This process is thought to proceed through a mechanism quite distinct from other metallacycle-mediated “alkyne”–aldehyde cross-coupling reactions. Ru-catalyzed dimerization of acetylene is reasoned to first result in the formation of metallacyclopentadiene that then engages the aldehyde in C–C bond-formation.¹¹⁷ While the process was quite effective at selectively generating the C4–C5 (*Z*)-disubstituted alkene, it would have to later be isomerized to the requisite (*E*)-disubstituted olefin of the natural product. Nevertheless, this reaction proved to be part of an effective strategy to generate trienomycin A and F, as well as the core of cytotrienin A (not depicted).¹¹⁸

6. Alkyne–Epoxide Cross-Coupling

Introduction

While most metallacycle-mediated cross-coupling chemistry engages the π -system of reaction partners in the course of generating a metallacyclopentane-motif, Ni-catalysis has proven to be an effective means of accomplishing coupling reactions between alkynes and epoxides (Figure 30). While being distinct from other reactions discussed in this report, as

they are thought to proceed by way of oxametallocyclohexenes,¹¹⁹ this class of metallacycle-mediated cross-coupling has proven to be useful in natural product synthesis. General issues regarding selectivity are wholly focused on regioselectivity with respect to both coupling partners (*i.e.*, **A** – **D**). Currently, products of this reaction derive from C–C bond-formation at the unsubstituted carbon of the epoxide, with regioisomers being possible from C–C bond formation at either carbon of the alkyne (leading to homoallylic alcohols **A** and/or **B**).

A. Total syntheses of Amphidinolide T1 and T4

The amphidinolides are a family of marine-derived natural products that have been shown to have a diverse array of potent cytotoxic properties.^{120, 121} Amphidinolide T natural products surfaced as interests to the Jamison group, perhaps due to their expectation that recently developed Ni-catalyzed transformations may be particularly effective at addressing a subset of the structural motifs associated with them.^{122, 123} In particular, Jamison approached the total syntheses of amphidinolides T1 and T4 with the planned use of two unique Ni-catalyzed C–C bond-forming processes: (1) an alkyne–epoxide cross-coupling, and (2) macrocyclization by alkyne–aldehyde coupling (Figure 31A). As illustrated in Figure 31B, the metallacycle-mediated cross-coupling reactions that were effectively wielded to accomplish the total syntheses of these two amphidinolides embrace the use of conjugated alkynes in C–C bond-formation – such alkynes are known to participate in Ni-catalyzed coupling reactions with a high degree of regioselectivity.¹¹⁹ Interestingly, in one of these coupling reactions the authors describe the chemoselective functionalization of a diyne. When diyne **77** was coupled to epoxide **75**, the homoallylic alcohol **78** was obtained in 40–44% yield. While the ¹H NMR spectrum of the crude material indicated some polymerization of the diyne (the limiting reagent), the authors reported that no evidence was found for engaging the TMS-alkyne in the Ni-catalyzed coupling process.

7. Alkene–Imine Cross-Coupling

Introduction

Metallacycle-mediated alkene–imine cross-coupling is a relatively complex process, as issues concerning regioselectivity (with respect to the alkene) and facial selectivity (with respect to both coupling partners) are coupled to the problem of engaging a coupling partner that typically is not highly reactive in metallacycle-mediated coupling chemistry (substituted alkenes) (Figure 32). To date, simple diastereoselection has been observed to highly favor the *anti*-stereoisomers **A** and **B** over the *syn*-isomers **C** and **D**.

As previously discussed in the context of alkoxide-directed alkene–alkyne coupling (Figure 11B), this class of metallacycle-mediated cross-coupling has been particularly effective with allylic alcohols.^{124–127} In such cases, alkoxide-directed metallacycle-mediated cross-coupling is followed by elimination to afford a homoallylic amine (Figure 33). While allylic metals are frequently employed to gain access to homoallylic amines, this class of coupling reaction provides a complementary pathway for the synthesis of such products that does not require the intermediacy of an allylic organometallic reagent and that can deliver products

that possess alkene substitution and stereochemistry not easily attainable with allylmetal addition chemistry.^{128, 129}

A. Total Synthesis of Alkaloid (–)-205B

Alkaloid (–)-205B is a representative member of a large class of alkaloids isolated by Professor Daly in his decades long investigation of natural products from neotropical frogs (Figure 34A).¹³⁰ It is unique among the natural product class in its ring structure and substitution and, while little is known about the biological activity of this agent, the unnatural antipode (prepared by Toyooka)¹³¹ was found to inhibit the $\alpha 7$ nicotinic acetylcholine receptor in a selective fashion.¹³² In a program that began with the development of metallacycle-mediated alkene–imine coupling chemistry,^{124, 125, 133} the Micalizio laboratory embraced (–)-205B as a target for synthesis.¹³⁴ As illustrated in Figure 34B, their efforts focused on chemoselective union of the chiral allylic alcohol **80** with a TMS-imine generated *in situ* from aldehyde **79** (by treatment with LiHMDS at low temperature). Notably, this variation of alkene–imine coupling proved to be enantiospecific and stereoselective, furnishing the homoallylic primary amine **81** in 57% yield as a single diastereomer, single olefin isomer, and with complete retention of absolute stereochemical information.

B. Total Synthesis of 7-exomethylene Indolizidine 223D

This target (Figure 35A) is a natural product analog and has been included to highlight an interesting chemoselectivity associated with metallacycle-mediated alkene–imine coupling. As illustrated in Figure 35B, the Micalizio laboratory coupled the allylic alcohol **82** with imine **83** as a means to generate homoallylic amine **84**. Here, bond-formation was dictated by the allylic alcohol rather than the allylic silane (*i.e.*, no product of aza-Sakurai allylation was observed).¹³⁵ This chemoselective metallacycle-mediated cross-coupling set the stage for an acid-mediate cyclization cascade that, in one step, resulted in the formation of the target with 20:1 diastereoselectivity.

8. Metallacycle-mediated Cross-Coupling by [2+2+1]

Introduction

Among the most widely employed metallacycle-mediated C–C bond-forming reactions in natural product synthesis is the Pauson-Khand reaction – a process that forges cyclopentenones by metallacycle-mediated alkene–alkyne coupling followed by carbonylation of the intermediate metallacyclopentene (Figure 36). To date, the vast majority of these applications have been conducted in *intra*- rather than *intermolecular* settings.¹³⁶ That said, there have been notable examples of the use of intermolecular Pauson-Khand reactions in natural product synthesis. These processes are, as illustrated in the bottom portion of Figure 36, quite complex. Not only does one need to confront the challenge of engaging substituted alkenes in the key metallacyclopentene-forming step, there is the ever-present challenge of simultaneously controlling regioselectivity in the functionalization of both coupling partners, as well as addressing π -facial selectivity. In selecting examples that highlight cross-coupling-based Pauson-Khand reactions in natural product synthesis,

attention has been paid to highlight those that use coupling partners more complex than ethylene.^{137–139}

A. Formal Total Synthesis of Brefeldin A

An early example of the use of intermolecular Pauson-Khand annulation in the context of natural product synthesis appeared in Greene's formal total synthesis of brefeldin A (Figure 37A).¹⁴⁰ Here, the authors pursued application of their recently developed diastereoselective version of the intermolecular Pauson-Khand reaction to establish the cyclopentane core of the natural product. As depicted in Figure 37B, union of chiral TMS-alkyne **85** with excess norbornadiene **86** resulted in the formation of cyclopentenone **87** in 82% yield (dr = 24:1).

B. Total Synthesis of Asteriscanolide

Asteriscanolide is a cyclooctane-containing sesquiterpene lactone that served as a target of interest to the Krafft laboratory (Figure 38A).^{141, 142} To address the cyclopentane motif of the natural product, they explored the use of an intermolecular Pauson-Khand reaction between propene (**88**) and alkynoate **89** (Figure 38B). The authors reported the generation of cyclopentenone **90** in 92% yield. Regioselectivity for the annulation process was rationalized by electronic and steric arguments, respectively.^{143, 144} The authors noted that the Pauson-Khand reaction was not successful with isobutene or allylic thioalkyl derivatives. As such, the authors found a different pathway for installing the desired quaternary center of the targeted 5-membered ring (by enolization of **90** and subsequent methylation).

C. Total Synthesis of (–)-Terpestacin

While previously discussed in the context of metallacycle-mediated alkyne-aldehyde cross-coupling, Jamison's synthesis of (–)-terpestacin (Figure 39A)^{108, 109} also featured an intermolecular Pauson-Khand reaction. As illustrated in Figure 39B, TMS-acetylene (**92**) was coupled to stereochemically defined dihydrofuran **91** to deliver the cyclopentenone product **93** as a single isomer in 51% yield.

D. Total Synthesis of 13,14-Dehydro-12-Oxo-Phytodienoic Acids (deoxy-J₁-phytoprostanes)

In efforts to understand whether recently discovered deoxy-J₁-phytoprostanes (Figure 40A) are markers of oxidative stress or are biologically active stress metabolites, the Mueller laboratory pursued the total syntheses of members of this class.¹⁴⁵ Here, they explored the utility of an asymmetric version of the Pauson-Khand annulation whereby TMS-acetylene was first converted to the chiral Co-complex **94**. Subsequent reaction with norbornadiene generated cyclopentenone **95** in 96% yield and with 99% ee.

E. Total Synthesis of (+/-)-Axinellamines A and B

As part of a program aimed at accomplishing the syntheses of members of the bioactive pyrrole-imidazole marine alkaloid family, the Baran group described an elegant and scalable synthesis of axinellamines A and B (Figure 41A).¹⁴⁶ Here, they demonstrated the ability to accomplish a stereo- and regioselective Pauson-Khand-based coupling reaction between the bis-TMS-ether of (*E*)-butene-1,4-diol (**96**) and the propargylic Boc-protected amine **97**. Their studies led to the discovery of a beneficial role for ethylene glycol in this process and

secured a stereoselective entry to cyclopentenone **98** as the first step of their total synthesis campaign.

9. Metallacycle-mediated Cross-Coupling by [2+2+2]

Introduction

The use of metallacycle chemistry for the union of three unsaturated systems has been known since the middle of the 20th century with Reppe's pioneering report on the Ni-catalyzed trimerization of acetylene for the synthesis of benzene (Figure 42A).⁵ While metallacycle-mediated cross-coupling chemistry has taken many different paths that diverge from Reppe's reaction as a means to accomplish a great variety of coupling processes (many have been presented earlier in this Report), there remains great interest in the development of [2+2+2] chemistry for regio- and stereoselective cross-coupling. With the advent of new metal-promoted or -catalyzed transformations of this type, a wide range of π -systems have been found to participate in related processes, and methods have since been described for the synthesis of a range of carbo- and heterocyclic systems. The proposed mechanisms for these processes are typically based on one of two pathways that diverge from an intermediate metallacyclopentadiene (or related structure) by either: (1) insertion (carbometalation) and reductive elimination, or (2) [4+2] followed by cheletropic extrusion (Figure 42B). Given that our focus is on the application of various metallacycle-mediated cross-coupling reactions in natural product synthesis, we will not discuss mechanistic intricacies associated with each application, unless deemed appropriate. Also, we note that the application of intermolecular versions of [2+2+2] annulation chemistry in natural product synthesis typically takes the form of bimolecular, rather than trimolecular, coupling (Figure 42C).

This section will be organized by the nature of the π -systems used in the annulation process, beginning with alkyne + alkyne + alkyne and finishing with annulation chemistry that employs an alkene as one of the coupling partners. We note that [2+2+2] chemistry has been the focus of numerous reviews and, as such, we do not aim to be comprehensive in this presentation of the application of [2+2+2] reactions to natural product synthesis. Rather, we share some historic and recent examples that provide a glimpse into the power that such chemistry has for cross-coupling.^{147, 148}

9.1. [Alkyne + Alkyne + Alkyne]

Any discussion of the role of [2+2+2] chemistry in natural product synthesis should begin with the impressive contributions of Professor Vollhardt.¹⁴⁹ His research group pioneered the development of Co-mediated [2+2+2] annulation chemistry and has described a number of total syntheses where this reactivity plays a central role. Two syntheses will be presented to highlight particular features of the annulation: (1) the total synthesis of estrone, and (2) the synthesis of the protoberberine nucleus.

A. Total Synthesis of Estrone—Vollhardt's synthesis of estrone is widely considered to be a classic in natural product synthesis, where a metallacycle-mediated coupling reaction played a profound role in accessing the steroid nucleus (Figure 43A).^{6, 150, 151} Co-catalyzed coupling of bis-trimethylsilyl acetylene (**99**) with the D-ring-containing diyne **100** was

observed to proceed with chemoselectivity, engaging the diyne in [2+2+2] and generating benzocyclobutene **101** (Figure 43B). Under the reaction conditions, benzocyclobutene **101** was found to undergo electrocyclic ring opening to generate a substituted *ortho*-xylylene (**102**) that subsequently participated in a stereoselective intramolecular Diels-Alder reaction *en route* to **103**, the final product generated in this process and isolated in 71% yield. While demonstrating an early example of [2+2+2] chemistry in natural product synthesis, this clever application avoided any concerns with regioselectivity due to the symmetry of **99**. Subsequent steps in Vollhardt's synthesis were used to differentiate the two trimethylsilyl groups located on the steroidal A-ring.

B. Synthesis of the Protoberberine Nucleus—Shortly following their triumph in applying Co-mediated [2+2+2] annulation for the synthesis of estrone, Vollhardt and coworkers described a variant of [2+2+2] chemistry in the context of a synthesis of the protoberberine nucleus (Figure 44A).¹⁵² As illustrated in Figure 44B, annulation between the TMS-alkyne-containing diyne **104** and alkyne **105** promoted by one equivalent of CpCo(CO)₂ produced the tetracycle **106** in 58% yield as a single regioisomer. Here, the TMS-group of alkyne **105** was reasoned to play a critical role in the regiochemical course of the [2+2+2] reaction.

C. Total Synthesis of Sporolide B—In efforts stimulated by the unprecedented molecular structures of the sporolides, natural products isolated from the marine actinomycete *Salinospora tropica*,¹⁵³ Professor Nicolaou and coworkers pursued the application of a highly convergent metallacycle-mediated coupling process to gain access to a late stage intermediate in their total synthesis of sporolide B (Figure 45A).^{154, 155} As illustrated in Figure 45B, Ru-catalyzed coupling of the terminal alkyne **107** with the chlorinated diyne **108** proceeded to deliver **109** in 87% yield as a single regioisomer – the product derived from selective reaction of alkyne **107** at the less hindered C–Ru bond of the metallacyclopentadiene (generated from **108**) where alkyne **107** is oriented in such a way to minimize unfavorable steric interaction with ligands at the Ru-metal center.

D. Total Synthesis of Alcyopterosin A—In efforts focused on exploring the utility of their recently described metalative Reppe reaction, Professor Sato's research group described the total synthesis of alcyopterosin A (Figure 46A).¹⁵⁶ As illustrated, their synthesis employed a Ti-mediated coupling of diyne **111** to alkynoate **110** – a process that generated the bicyclic product **112** in 73% yield (Figure 46B). Here, the mechanistic course of the annulation was reasoned to be distinct from the paths first introduced in this section of the Report (Figure 42B). As illustrated in Figure 46C, initial reaction between the Ti-alkyne complex of **110** with **111** is proposed to generate a functionalized metallacyclopentadiene where regioselection mirrors that which had been described earlier for alkyne–alkyne coupling reactions (Figure 3A). Moving on, the metallacycle engages the pendant alkyne in an intramolecular [4+2] cycloaddition. It has been proposed that the resulting bridged bicyclic metallacyclopentene then rearranges by elimination and isomerization to deliver a benzyltitanium species, protonation of which then delivers the observed product of [2+2+2] and sets the stage for completion of a total synthesis of alcyopterosin A.

E. Total Synthesis of Hyellazole—In 2002 Witulski and coworkers described an approach to substituted carbazoles based on crossed [2+2+2] annulation chemistry and, in the course of these studies, described a convergent synthesis of hyellazole (Figure 47A).¹⁵⁷ As depicted in Figure 47B, their key step was the Rh-catalyzed coupling between diyne **113** and alkyne **114** *en route* to **115**. The reaction proceeded with good efficiency (89%) and outstanding regioselectivity (30:1), while demonstrating the utility of a metallacycle-mediated [2+2+2] annulation with heteroatom-substituted alkynes for the synthesis of carbazoles.

9.2. [Alkyne + Alkyne + Nitrile]

This version of the [2+2+2] annulation process has found numerous applications in natural product synthesis. The first of these is discussed below and is followed by more recent examples.

A. Total Synthesis of Vitamin B₆—Shortly after their report that described the synthesis of steroids by Co-mediated [2+2+2] annulation between an alkyne and a diyne, the Vollhardt group accomplished a total synthesis of vitamin B₆ that demonstrated the potential of a heteroatom analogue of their Co-mediated process to forge densely functionalized pyridines (Figure 48A).¹⁵⁸ In a very clever strategy, Vollhardt designed the synthesis to proceed through union of the symmetrical diyne **116** with acetonitrile (**117**). Due to the symmetry of **116**, there is no opportunity to deliver a regioisomer in the [2+2+2]. Fortunately, after annulation, the pyridine product was found to undergo selective mono-destannylation on purification to deliver **118** in 45% yield. Notably, this basic strategy for pyridine synthesis, that employs a symmetric diyne and a nitrile, has been adopted for the synthesis of other alkaloid targets.¹⁵⁹

B. Total Synthesis of (+/-)-Lysergene—Moving forward from their vitamin B₆ synthesis, the Vollhardt laboratory designed an alkyne + alkyne + nitrile metallacycle-mediated cross-coupling reaction for the synthesis of lysergene (Figure 49A).¹⁶⁰ The key annulation reaction is highlighted in Figure 49B and features the coupling of an alkynyl nitrile (**119**) with TMS-alkyne **120**. In comparison to their earlier work targeting vitamin B₆, this effort was substantially more complex owing to the unsymmetric nature of the TMS-alkyne coupling partner (**120**). Fortunately, they were able to employ a Co-promoted [2+2+2] annulation to produce the tetracyclic products **121** and **122** in a combined 49% yield. The desired regioisomer was found to readily desilylate *en route* to producing **121** in a 38% isolated yield.

C. Synthesis of Lavendamycin Methyl Ester—Lavendamycin is an antitumor antibiotic isolated from *Streptomyces lavendulae*¹⁶¹ that was shown to have activity against several cancer cell lines as well as topoisomerase 1 (Figure 50A).¹⁶² In efforts targeting the synthesis of lavendamycin, Nissen and Detert described a variant of an alkyne/alkyne/nitrile [2+2+2] annulation that employed an alkynyl sulfonamide.¹⁶³ As illustrated in Figure 50B, a Ru-catalyzed [2+2+2] annulation between diyne **123** and methyl cyanoformate (**124**) resulted in a highly efficient and regioselective [2+2+2] process leading to production of **127** in 92% yield. Mechanistically distinct from examples described in this section, the origin of

regioselection was proposed to derive from the [2+2] addition product of methyl cyanoformate (**124**) with an intermediate metallacycle. Preferential addition occurs to the Ru–C- α bond to form the least hindered cycloadduct. Interestingly, Cp*RuCl(cod) was uniquely effective in accomplishing this regioselective annulation reaction (the authors have moved forward with similar annulation reactions in natural product synthesis).¹⁶⁴

D. Total Synthesis of (+)-Complanadine A—Complanadine A is a fascinating alkaloid that possesses an interesting structure and displays unique and potentially valuable medicinal properties, in particular the ability to induce the secretion of neurotrophic factors from 1321N1 cells and result in the differentiation of PC-12 cells (Figure 51A).¹⁶⁵ Recently, the Siegel laboratory described a highly convergent assembly of complanadine A by application of a sequence of alkyne/alkyne/nitrile-based [2+2+2] annulation reactions, defining perhaps one of the most elegant applications of this type of metallacycle-mediated cross-coupling reaction in natural product synthesis.¹⁶⁶ As illustrated in Figure 51B, CpCo(CO)₂-mediated union of **128** with **129** proceeded in 82% yield and delivered the desired pyridine with 25:1 regioselectivity. Moving on, they addressed the synthesis of the second pyridine of complanadine A with another application of an alkyne/alkyne/nitrile [2+2+2] annulation that united the two polycyclic hemispheres of the target. In this latter case (*i.e.*, union of alkyne **131** with alkynyl nitrile **132**), modified reaction conditions were required to favor the formation of the desired regioisomer.

Overall, this [2+2+2] annulation strategy has since been utilized to prepare lycodine (and analogs thereof) with the aim of evaluating its effects on neuronal growth alongside its pseudosymmetric dimer, complanadine A.^{167, 168}

9.3. [Alkyne + Alkyne + Isocyanate]

Among the collection of contributions that blossomed from the Vollhardt group, it was found that the Co-mediated [2+2+2] annulation chemistry can be conducted with isocyanates as one of the participating π -systems.¹⁶⁹ Specifically, Vollhardt described the intermolecular coupling of 5-isocyanatoalkynes with alkynes *en route* to the formation of 5-indolizinones (Figure 52). The reaction was found to proceed with good chemo- and regioselectivity when TMS-alkynes are used – the silyl group emerges α to the amide linkage.

A. Formal Total Synthesis of Camptothecin—Camptothecin is a pentacyclic alkaloid that possesses potent cytotoxic activity against a variety of tumor cell lines, and synthetic derivatives of this agent have been demonstrated to be useful in the clinic (Figure 53A). In efforts that were sprung from their development of an isocyanate variant of their Co-catalyzed [2+2+2] annulation reaction, the Vollhardt laboratory demonstrated the utility of this reaction process in the formal total synthesis of camptothecin.¹⁶⁹ As illustrated in Figure 53B, Co-catalyzed annulation between isocyanate **134** and TMS-alkyne **135** resulted in the formation of the indolizinone **136** – a species that was subsequently converted into an intermediate that had previously been employed in a total synthesis of camptothecin.

9.4. [Alkyne + Alkene + Isocyanate]

In a surprising turn that diverges from the [2+2+2] reaction of isocyanatoalkynes, Professor Rovis described an interesting version of this type of annulation with alkenyl isocyanates. As illustrated in Figure 54, Rh-catalyzed [2+2+2] between a terminal alkyne and an alkenyl isocyanate delivers an annulation product (**139**) that has different connectivity than what was previously described by Vollhardt in his Co-catalyzed annulation reaction. Rovis has proposed a mechanism whereby initial metallacycle-mediated alkyne–isonitrile coupling is followed by CO migration, alkene insertion and reductive elimination.

A. Total Synthesis of (+)-Lasubine II—During the course of their development of the enantioselective alkenyl isocyanate – alkyne coupling reaction, the Rovis laboratory investigated application of this technology to the total synthesis of (+)-lasubine II (Figure 55A).¹⁷⁰ Due to the CO-migration associated with this enantioselective [2+2+2] annulation, the bonds targeted for formation with this process are a bit different than typically seen in [2+2+2] annulation methods. Here, the four C–C bonds highlighted in Figure 55A were those that would derive from the annulation process. As illustrated in Figure 55B, union of alkenyl isocyanate **141** with alkyne **142** established the entire carbon skeleton of the natural product, producing **143** in 62% yield and 98% ee. This intermediate was converted to (+)-lasubine II in just three additional steps.

B. Total Synthesis Alkaloid (–)-209D—In studies springing from their initial discovery of Rh-cat. [2+2+2] annulation between terminal alkynes and alkenyl isocyanates, where the vinylogous amide product was favored when aryl-alkynes were employed as coupling partners, the Rovis laboratory targeted the development of a variant of this annulation method that would be effective with alkyl-substituted terminal alkynes.¹⁷¹ In the course of these studies, they demonstrated the utility of this method in the context of a concise, asymmetric total synthesis of alkaloid (–)-209D (Figure 56A). As illustrated in Figure 56B, union of **144** with terminal alkyne **145**, under the action of a chiral Rh-catalyst derived from a distinct phosphoramidite ligand than previously explored in the context of the lasubine II synthesis (Figure 55B), resulted in the formation of the indolizidine **146** in 66% yield and 91% ee (the unsaturated lactam product corresponding to **140** in Figure 54 was seen as a minor byproduct in this reaction, with the vinylogous lactam being favored in a ratio of 6:1).

9.5. [Alkyne + Alkyne + Alkene]

The final collection of methods to be discussed in this section of the Report are based on metallacycle-mediated intermolecular [2+2+2] annulation methods that engage two alkynes and one alkene during the course of generating a cyclohexadiene motif (Figure 57). In all cases where such chemistry has been employed in the context of natural product synthesis, these annulation procedures take the form of cross-coupling a suitably functionalized enyne with an alkyne.

A. Formal Total Synthesis of γ -Lycorane—An early example of the use of metallacycle-mediated cross-coupling between an enyne and an alkyne appeared in Vollhardt's formal total synthesis of the alkaloid γ -lycorane (Figure 58A).¹⁷² Here, their efforts were focused on the use of an enamine double bond in the [2+2+2] annulation,

realizing the union of **147** with bis-TMS-acetylene **99** – a process that produced **148** in 65% yield. Related to other elegant synthesis strategies devised by Professor Vollhardt, there was no issue with regioselectivity in this annulation process due to the symmetry of **99**.

B. Formal Total Synthesis of Strychnine—Since R. B. Woodward's pioneering synthesis of strychnine,^{173, 174} this alkaloid has stood as a classic target in natural product synthesis (Figure 59A).^{175–185} Moving forward with the development of methods for Co-mediated [2+2+2] annulation between enynes and alkynes, Vollhardt's group demonstrated the ability to employ an indole double bond in the annulation process and highlighted the application of this coupling chemistry in the context of a formal total synthesis of strychnine.^{186, 187} As illustrated in Figure 59B, union of **149** with acetylene (**71**) delivered the tetracyclic product **150** in 46% yield. As has previously been demonstrated in numerous Vollhardt-designed synthesis strategies employing [2+2+2] annulation chemistry, the key annulation employed in the strychnine campaign avoids any issues with regioselectivity due to the symmetry of the alkyne coupling partner (acetylene).

C. Total Synthesis of (2S)-Hydroxy-3,4-Dehydroneomajucin—In efforts focused on the exploration of chemoselectivity in their hydroxyl-directed alkyne–alkene and alkyne–alkyne coupling reactions, the Micalizio laboratory discovered a highly regio- and stereoselective [2+2+2] annulation *en route* to angularly substituted hydrindanes.^{188–191} This reaction played a central role in their recently described synthesis of (2S)-hydroxy-3,4-dehydroneomajucin – a molecule that belongs to a larger class of sesquiterpenes that have been shown to possess potent and unique activity as neurotrophic agents (Figure 60A).¹⁹² Here, union of enyne **151** with the unsymmetrical alkyne **152** proceeded to deliver the angularly substituted hydrindane **153** in 73% yield (rs 20:1; ds 20:1). This process is unique with respect to other intermolecular enyne + alkyne [2+2+2] reactions employed in natural product synthesis in that the alkyne component is unsymmetrical and the annulation proceeds with exquisite regioselectivity, while also establishing an angular quaternary center (C9). In addition to moving this material forward to complete the first total synthesis of (2S)-hydroxy-3,4-dehydroneomajucin, the Micalizio laboratory also demonstrated the ability to advance this intermediate to (1*R*,1*OS*)-2-oxo-3,4-dehydroneomajucin and (–)-jiadifenin.

10. Other Intermolecular C–C Bond-Forming Reactions that Derive from the Chemistry of Metallacyclopentanes

Introduction

At the start of this Report, we set the stage for a discussion that was centered on an inclusive definition of metallacycle-mediated cross-coupling. This perspective united crossed metathesis chemistry with the diverse collection of coupling reactions that are thought to proceed through metallacyclopentane-like intermediates, while also including an example of a process that is thought to proceed by way of an oxametallacyclohexene intermediate (Jamison's alkyne–epoxide coupling). While most of the syntheses described earlier clearly highlight intermolecular C–C bond formation during the metallacycle-forming step, the latter section on [2+2+2] annulation chemistry presents applications where the sequence of events is less clear. Perhaps in a number of cases (not including the process depicted in

Figure 60), the metallacyclopentane-forming step occurs intramolecularly, with the intermolecular process taking place after formation of the metallacyclopentane intermediate. We recognize the ambiguity with these processes, and decided to include them due to the overall intermolecular nature of the metallacycle-mediated transformations. Because of this ambiguity, we are compelled to share several examples of natural product syntheses that employ a metallacycle-mediated C–C bond-forming event, but where the intermolecular processes are proposed to occur after an initial metallacycle-mediated cyclization. This collection of reactions is viewed as somewhat off-topic, but we have selected to highlight a few modern examples that speak to a different role of metallacycle chemistry in intermolecular C–C bond-formation.

A. Total Syntheses of Kainoids

Professor John Montgomery has been a leader in the development of Ni-catalyzed metallacycle-mediated C–C bond-forming reactions and the use of these processes in natural product synthesis. One of his early contributions was the discovery of a Ni-catalyzed cyclization that is terminated by a cross-coupling event with another organometallic species. In this way, his annulation chemistry provides a means to forge two C–C bonds, one from the metallacycle-forming intramolecular reaction and one from the capture of this species by cross-coupling with a different organometallic species. A beautiful collection of syntheses highlight the broad generality of this type of chemistry while also establishing a highly stereoselective entry to kainoid natural products (Figure 61A).

A general depiction of the reaction process that has been employed in these syntheses is presented in the top section of Figure 61B, and the specific examples reported in the context of total syntheses follow [for (–)-kainic acid, (+)- α -allokainic acid, and isodomoic acids G and H].^{193–196} Overall, this collection of examples highlights the strategic utility of Montgomery's Ni-catalyzed transformations to address challenging and complex problems in stereoselective synthesis. While not selected for discussion here, Montgomery has also employed related strategies for the synthesis of (+)-testudinariol A (by allene–aldehyde cyclization and coupling with Me_2Zn) and (+/–)-deformyl-isogeissoschizine (by terminal alkyne– α,β -unsaturated imide cyclization and coupling with Me_2Zn).^{197, 198}

B. Total Synthesis of Carbacyclin

Professor Sato took the early lead in developing metallacycle-mediated coupling chemistry promoted by reagents prepared from the combination of $\text{Ti}(\text{O}i\text{-Pr})_4$ and two equivalents of a Grignard reagent (reaction conditions originally used for the Kulinkovich reaction).^{199, 200} Among the many contributions that Professor Sato made to this area of reaction methodology were collections of intramolecular metallacycle-forming processes that took advantage of the resulting titanacyclopentane-type intermediate in subsequent bond-forming processes. One of these was highlighted in the total synthesis of (+/–)-carbacyclin (Figure 62A).^{201–203} As depicted in Figure 62B, Ti-promoted intramolecular diene cyclization was followed by isomerization to a Ti-enolate and intermolecular aldol reaction. The reaction process was concluded with intramolecular addition of the resulting organometallic species to the pendant ester (intramolecular nucleophilic acyl substitution – “INAS”). This elegant

cascade establishes both rings of the carbacyclin structure and the functionalized side chain in a single step.

C. Total Synthesis of 9-Hydroxysargaquinone

Professor Whitby has established a collection of strategies for C–C bond formation that stem from the reactivity of zirconacyclopentane intermediates.^{204, 205} As illustrated in Figure 63, a lithiated allylic chloride is employed in initial nucleophilic addition to Zr and the resulting ate-complex undergoes ring expansion by a 1,2-shift to generate a zirconacyclohexane. This species, also an allylzirconium, can be used in subsequent bond forming reactions – i.e. addition to an aldehyde.

In 2005, Whitby described a zirconium-mediated synthesis of 9-hydroxysargaquinone that proceeded through a zirconacycle-mediated coupling process that generated three C–C bonds of the target structure (Figure 64A).²⁰⁶ While we have excluded summarizing natural product syntheses that proceed by simple metallacycle-mediated addition of Grignard reagents or organolithium species to an alkene or alkyne, we have included the synthesis of 9-hydroxysargaquinone described by Whitby because of the multicomponent nature of the process. As illustrated in Figure 64B, coupling of tributylstannyl propyne (**166**) to geranial (**167**) proceeded to deliver the functionalized tetraene **168** possessing a vinyltin species suitable for subsequent functionalization. Notably, this process demonstrated the ability to selectively expand the zirconacyclopentene intermediate by migration of the sp^3 , rather than sp^2 , carbon.

D. Total Synthesis of (+/-)-Acetoxodontoschismenol

In pursuits focused on the total synthesis of acetoxodontoschismenol, Whitby pursued a different variant of this multi-component coupling reaction (Figure 65A).²⁰⁷ Here, intramolecular diene cyclization was used as the initial step to generate the reactive zirconacyclopentane species – an intermediate whose carbenoid-based ring expansion would not be as straightforward as the example previously described in the context of 9-hydroxysargaquinone. As illustrated in Figure 65B, the hybridization of both carbons bound to zirconium is sp^3 , setting up a question regarding selectivity of the subsequent carbenoid insertion step. Fortunately, Whitby observed product derived from migration of the neopentyl sp^3 carbon, followed by allylation upon addition of the α,β -unsaturated aldehyde and, finally, iodination of the remaining sp^3 C–Zr bond. Overall, the metallacycle-mediated coupling process delivered the product in 65% yield, whereby the quaternary center resident in the cyclopentane was established with 4:1 selectivity.

E. Total Synthesis of Fluvirucin B₁

Admittedly not quite fitting seamlessly in this section of the Report, we conclude with a discussion that highlights the application of Professor Hoveyda's Zr-catalyzed carbomagnesiation chemistry in natural product synthesis. The general process, first described in 1983 for addition of ethylmagnesium bromide to simple alkenes,²⁰⁸ features the use of Cp_2ZrCl_2 in a catalytic process for net regioselective hydroxyalkylation (Figure 66).^{209, 210}

In 1995, the Hoveyda group described a route to fluvirucin B₁ that employed two variations of their Zr-catalyzed carbomagnesiation process (Figure 67A).^{211, 212} As illustrated in Figure 67B, one of these employed the diastereoselective ethylmagnesiation of an allylic alcohol (**172**) and was terminated by reaction with a tosylated aziridine. The other demonstrated the utility of their catalytic asymmetric ethylmagnesiation. Here enantioselective addition to 3-dihydrofuran (**174**) resulted in an organometallic intermediate that underwent ring-opening elimination to deliver homoallylic alcohol **175** with outstanding levels of enantioselectivity.

11. Intermolecular Kulinkovich Reactions in Natural Product Synthesis

The use of the Kulinkovich reaction in natural product synthesis was reviewed in 2012 and, as such, we will only highlight some recent examples that employ intermolecular Kulinkovich reactions in the context of natural product synthesis.¹³

A. Total Synthesis of (+)-Spirolaxine Methyl Ether

In 2007, Professor Phillips described the application of the intermolecular Kulinkovich reaction for subunit coupling in the total synthesis of (+)-spirolaxine methyl ether (Figure 68A).²¹³ As illustrated in Figure 68B, these efforts highlighted the union of terminal alkene **176** with the chiral lactone **177** *en route* to the hydroxycyclopropane product **178**. Exposure of this product to the combination of Fe(NO₃)₃ and Bu₃SnH resulted in ring opening to generate the corresponding ketone, and subsequent desilylation resulted in a triol that spontaneously cyclized to the spiroketal-containing product **179**.

B. Total Synthesis of Demethyl (C-11) Cezomycin

Recently, a related approach to subunit coupling was described in Wu's total synthesis of the anti-fungal antibiotic demethyl (C-11) cezomycin (Figure 69A).²¹⁴ Here, intermolecular Kulinkovich reaction between ester **180** and terminal alkene **181** was employed to generate hydroxycyclopropane product **182** that, in subsequent steps, was cleaved by the action of Fe(NO₃)₃ and advanced to the central spiroketal motif of the target (Figure 69B).

12. Summary and Outlook

Metallacycle-mediated cross-coupling is broadly defined here as an intermolecular C–C bond-forming process that proceeds by way of a metallacyclic intermediate. Since the middle of the 20th century, such chemistry has grown far beyond simple alkyne trimerization, and has established a large collection of highly selective synthetic methods that can be employed to realize unique retrosynthetic relationships of relevance to the total synthesis of terpenes, alkaloids and polyketides. Coupling partners can now include a variety of participating π -systems, and intermolecular C–C bond formation can occur during the formation of a metallacyclic intermediate, or after – where the metallacycle-forming step is first embraced in an intramolecular fashion. It is becoming increasingly clear that the transformations accessible with this style of chemistry are not only complex, offering the opportunity to forge numerous C–C bonds and stereochemical relationships in a single

reaction process, they are diverse and can be wielded to address a large variety of structural challenges in synthetic organic chemistry.

Until recently, many reactions that we now consider “metallacycle-mediated cross-coupling” were characterized independently, with focus given to the nature of the metal employed, and/or whether a reaction component can be used in a substoichiometric fashion. We believe that unifying what can appear as a collection of disparate chemical transformations as belonging to a larger class of reactivity will have a beneficial pedagogical impact and define a robust foundation on which to build a bright future for this area of organometallic chemistry. With a focus on addressing problems in chemical synthesis, we believe that metallacycle-mediated cross-coupling will continue to define fertile ground for discovery, with advances enabling ever more efficient syntheses of exquisitely complex targets.

While there is much cause for enthusiasm regarding the future of metallacycle-mediated cross-coupling, there remain many barriers that we believe should be addressed. Future contributions that would have a profound impact on this area include those that would: (1) provide a means to move away from depending on the use of expensive, rare and toxic metals, (2) avoid the use of “exotic” and costly ligands, (3) realize reaction processes that are user-friendly (i.e. that do not require a rigorously anhydrous and anaerobic environment), and (4) establish a general and selective means of achieving a true “mix-and-match” future for the coupling of diverse, substituted, and functionalized π -systems – all while being chemo-, regio-, and stereoselective. The last 50 years of chemical research has established a robust foundation in this area and has offered numerous examples that reinforce the great value of metallacycle-mediated cross-coupling in total synthesis. We look forward to seeing this area of chemical reactivity continue to grow in a manner that greatly impacts the future of complex molecule synthesis.

Acknowledgments

The authors acknowledge funding for their program in metallacycle-mediated cross-coupling from the National Institutes of Health – GM080266.

Biographies

Natasha F. O'Rourke received her B.Sc. in Chemistry and Biology from St. Francis Xavier University (NS, Canada) in 2008 under the supervision of Dr. Manuel A. S. Aquino where she worked on the synthesis of diruthenium (II, III) and dirhenium (III, III) tetracarboxylates possessing biologically relevant ligands for potential application as metallotherapeutic agents. In 2014, she received her Ph.D. in Organic Chemistry and Chemical Biology from

the University of Victoria (BC, Canada) where she studied under the supervision of Dr. Jeremy E. Wulff. Her graduate studies focused on mechanistic investigation of orthogonal transformations of bis-vinyl ethers and on developing methods to access small molecule disruptors of the PD-1/PD-L1 interaction involved in metastatic cancer. In 2014, she moved to the United States where she joined the group of Prof. Glenn C. Micalizio at Dartmouth College (NH) as a postdoctoral research associate in the Department of Chemistry. Her work has focused on the development of new synthetic methods and strategies for natural product synthesis.

Matthew J. Kier received his B.A. in chemistry from Goucher College in 2006 under Professor George E. Greco where he worked on metal-catalyzed cycloaddition reactions. In 2010 he received an M.S. in chemistry from the University of California, Irvine under the supervision of Professor Christopher D. Vanderwal where he worked on the formal synthesis of porothramycins A and B. Currently, he is a graduate student in the Department of Chemistry at Dartmouth College where his research in the laboratory of Professor Glenn C. Micalizio is focused on developing new metallacycle-centered chemistry for applications in natural product total synthesis.

Professor Micalizio trained as a Fellow of the Helen Hay Whitney Foundation in the laboratories of Professor Stuart L. Schreiber at Harvard University (2001-2003), received his PhD at the University of Michigan (2001) after graduate studies in the laboratories of Professor William R. Roush, and completed undergraduate studies at Ramapo College of NJ (1996). He began his independent academic career as an Assistant Professor in the Department of Chemistry at Yale University (2003), was later recruited to join the Department of Chemistry at the Scripps Research Institute and, most recently Dartmouth College where he is currently the New Hampshire Professor of Chemistry. His research interests are focused on the development and application of new methods and synthesis strategies in organic chemistry and the application of these toward the discovery of molecules with interesting biological properties.

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Figure 1.
 Introduction to metallacycle-mediated cross-coupling.

A. Reactivity: Intra- vs Intermolecular settings

B. Regioselectivity

C. Diastereoselectivity

Figure 2.
General considerations – reactivity and selectivity.

A. Sato's Ti-mediated alkyne-alkyne coupling:

B. Micalizio's alkoxide-directed and non-directed alkyne-alkyne coupling:

Figure 3.
Ti-alkoxide-mediated alkyne-alkyne coupling.

A. Structure of callystatin A and the bond targeted for metallacycle-mediated cross-coupling:

— = bond targeted for metallacycle-mediated alkyne–alkyne cross-coupling.

B. Key metallacycle-mediated coupling step employed in Micalizio's synthesis:

Figure 4.
Total synthesis of callystatin A.

A. Structure of dictyostatin and the bond targeted for metallacycle-mediated cross-coupling:

* = bond targeted for metallacycle-mediated alkyne-alkyne cross-coupling.

B. Key metallacycle-mediated coupling step and subsequent reduction employed in Micalizio's synthesis:

Figure 5.
Formal total synthesis of dictyostatin.

A. Structure of virginiamycin M₂ and the bond targeted for metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkyne–alkyne cross-coupling.

B. Key metallacycle-mediated coupling step in Panek's synthesis:

Figure 6.
Total synthesis of virginiamycin M₂.

A. Structure of heronamide C and the bond targeted for metallacycle-mediated cross-coupling:

— = bond targeted for metallacycle-mediated alkyne-alkyne cross-coupling.

B. Key metallacycle-mediated coupling step in Kanoh's total synthesis:

C. Potential elimination pathway for intermediate titanacyclopentene:

Figure 7.
Total synthesis of the proposed structure of heronamide C.

A. Structure of geldanamycin and valerjesomycin and the bond targeted for metallacycle-mediated cross-coupling:

7 = bond targeted for metallacycle-mediated alkyne-alkyne cross-coupling.

B. Key metallacycle-mediated coupling step in Micalizio's function-oriented synthesis of geldanamycin-inspired Hsp90 inhibitors:

Figure 8.

Function-oriented synthesis – discovery of valerjesomycin as a paralog selective natural product-inspired Hsp90 inhibitor.

A. Early examples of reactivity between alkenes and alkynes were for cyclization chemistry:

B. General instability associated with metallacyclopentenenes: A central feature of Negishi's alkyne-alkyne coupling process.

Figure 9.

Early investigations of methods that proceed by way of metallacyclopentenenes.

Figure 10.
Ru-catalyzed Alder-ene reaction.

A. Takahashi's Cp₂Zr-mediated alkyne–allylic ether coupling: **B.** Micalizio's Ti-alkoxide-mediated alkyne–allylic alcohol coupling:(E)-selective coupling: (Z)-selective coupling:

Figure 11.
Group IV metal-mediated alkyne–allylic alcohol coupling.

A. γ -Lactone formation by Ru-catalyzed Alder-ene coupling: **B.** Alkyne-alkene coupling in Trost's total synthesis of (+)-ancepsenolide:

— = bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.

key metallacycle-mediated coupling reaction:

C. Alkyne-alkene coupling in Trost's total synthesis of (+)-solamin:

— = bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.

key metallacycle-mediated coupling reaction:

Figure 12.

Ru-catalyzed Alder-ene reaction for the synthesis of acetogenins.

A. Proposed structure of trocheliophorolide B:

= bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.

B. Ru-catalyzed Alder-ene coupling in the synthesis of trocheliophorolide B:

Figure 13.
Synthesis of the proposed structure of trocheliophorolide B.

A. Structure of callipeltoside A and deschlorocallipeltoside A:

= bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.

B. Ru-catalyzed Alder-ene coupling in Trost's synthesis of deschlorocallipeltoside A:

Figure 14.
Synthesis of deschlorocallipeltoside A.

A. Structure of alternaric acid and the bond targeted for construction by metallacycle-mediated cross-coupling:

$\rightleftharpoons$ = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.

B. Alkene–alkyne coupling in Trost's formal synthesis of alternaric acid:

Figure 15.
Synthesis of alternaric acid.

A. Structure of mycalamide A and the bond targeted for construction by metallacycle-mediated cross-coupling:

$\rightleftharpoons$ = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.

B. Alkene–alkyne coupling in Trost's formal synthesis of mycalamide A:

Figure 16.
Formal total synthesis of mycalamide A.

A. Structure of amphidinolide A and the bond targeted for construction by metallacycle-mediated cross-coupling:

— = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.
 = macrocyclization accomplished by ring-closing Alder-ene reaction.

B. Alkene–alkyne coupling in Trost's total synthesis of amphidinolide A:

Figure 17.
Total synthesis of amphidinolide A.

A. Structure of amphidinolide P and the bond targeted for construction by metallacycle-mediated cross-coupling:

--- = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.

B. Alkene–alkyne coupling in Trost's total synthesis of amphidinolide P:

Figure 18.
Total synthesis of amphidinolide P.

A. Structure of (–)-dactylolide and the bond targeted for construction by metallacycle-mediated cross-coupling:

↖ = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.
 ↗ = a "boronate Alder-ene" reaction was employed - not proposed to proceed by way of a metallacyclopentene.

B. Alkene–alkyne coupling in Lee's total synthesis of (–)-dactylolide:

Figure 19.
 Total synthesis of (–)-dactylolide.

A. Structure of bryostatin 16 and the bond targeted for construction by metallacycle-mediated cross-coupling:

$\curvearrowright$ = bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.

B. Alkene-alkyne coupling in Trost's total synthesis of bryostatin 16:

Figure 20.
Total synthesis of bryostatin 16.

A. Structure of lehualide B and the bond targeted for construction by metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.

B. Alkene-alkyne coupling in Micalizio's total synthesis of lehualide B:

Figure 21.
Total synthesis of lehualide B.

A. Structure of (–)-vittatalactone and the bond targeted for construction by metallacycle-mediated cross-coupling:

— = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.

B. Alkene–alkyne coupling in Micalizio's total synthesis of (–)-vittatalactone:

Figure 22.
Total synthesis of (–)-vittatalactone.

A. Structure of (+)-phorbasin C and the bond targeted for construction by metallacycle-mediated cross-coupling:

$\longleftrightarrow$ = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.

B. Alkene–alkyne coupling in Micalizio's total synthesis of (+)-phorbasin C:

Figure 23.
Total synthesis of (+)-phorbasin C.

Reductive alkyne–aldehyde cross-coupling:

Possible products of cross-coupling:

Figure 24.

Introduction to metallacycle-mediated alkyne–aldehyde cross-coupling.

A. Structure of (–)-terpestacin and the bond targeted for construction by metallacycle-mediated alkyne–aldehyde cross-coupling:

--- = bond targeted for metallacycle-mediated alkyne–aldehyde cross-coupling.

B. Alkyne–aldehyde coupling in Jamison's total synthesis of (–)-terpestacin:

Figure 25.
Total synthesis of (–)-terpestacin.

A. Structure of macbecin I and the bond targeted for metallacycle-mediated cross-coupling:

* = bond targeted for metallacycle-mediated alkyne-aldehyde cross-coupling.

B. Key metallacycle-mediated coupling step in Micalizio's synthesis of macbecin I:

Figure 26.
Total synthesis of macbecin I.

A. Structure of D-erythro-sphingosine and the bond targeted for metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkyne–aldehyde cross-coupling.

B. Key metallacycle-mediated coupling step in Montgomery's synthesis of D-erythro-sphingosine:

Figure 27.
Total synthesis of D-erythro-sphingosine.

A. Structure of bryostatin 7 and the bond targeted for construction by metallacycle-mediated cross-coupling:

— = bond targeted for metallacycle-mediated alkyne–aldehyde cross-coupling.

B. Alkyne–aldehyde coupling in Krische's total synthesis of bryostatin 7:

Figure 28.
Total synthesis of bryostatin 7.

A. Structure of trienomycin A and F and the bond targeted for construction by metallacycle-mediated cross-coupling:

--- = bond targeted for metallacycle-mediated alkyne–aldehyde cross-coupling.

B. Alkyne–aldehyde coupling in Krische's total synthesis of trienomycin A and F:

mechanistically distinct from previously discussed metallacycle-mediated "alkyne–aldehyde" coupling reactions:

Figure 29.
Total synthesis of trienomycin A.

Reductive alkyne–epoxide cross-coupling:

Possible products of cross-coupling:

Figure 30.

Introduction to metallacycle-mediated alkyne–epoxide cross-coupling.

A. Structure of amphidinolide T1 and T4 and the bond targeted for construction b; metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkyne–epoxide cross-coupling.
 = bond targeted for metallacycle-mediated alkyne–aldehyde macrocyclization.

B. Alkyne–epoxide coupling in Jamison's total syntheses of amphidinolide T1 and amphidinolide T4:

Figure 31.

Total synthesis of amphidinolide T1 and T4.

Reductive alkene–imine cross-coupling:

Possible products of cross-coupling:

Figure 32.

Introduction to metallacycle-mediated alkene–imine cross-coupling.

(E)-selective coupling: (Z)-selective coupling: **Figure 33.**

Alkoxide-directed metallacycle-mediated cross-coupling.

A. Structure of alkaloid (–)-205B and the bond targeted for construction by metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkene–imine cross-coupling.

B. Alkene–imine coupling in Micalizio's total syntheses of alkaloid (–)-205B:

Figure 34.
Total synthesis of alkaloid (–)-205B.

A. Structure 7-exomethylene indolizidine 223D and the bond targeted for construction by metallacycle-mediated cross-coupling:

B. Alkene-imine coupling in Micalizio's total syntheses of 7-exomethylene indolizidine 223D:

Figure 35.
Total synthesis of 7-exomethylene indolizidine 223D.

Pauson-Khand reaction:

Proposed mechanism (Magnus):

Possible products (assuming suprafacial addition to alkene):

Figure 36.

Intermolecular Pauson-Khand reaction – an annulation that proceeds by alkene–alkyne coupling.

A. Structure of brefeldin A and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.
 = bonds targeted for metallacycle-mediated carbonyl insertion.

B. Alkyne–alkene coupling in Greene's formal total syntheses of brefeldin A:

Figure 37.
Formal total synthesis of brefeldin A.

A. Structure of asteriscanolide and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bond targeted for metallacycle-mediated alkyne-alkene cross-coupling.
 = bonds targeted for metallacycle-mediated carbonyl insertion.

B. Alkyne-alkene coupling in Krafft's total syntheses of asteriscanolide:

Figure 38.
Total synthesis of asteriscanolide.

A. Structure of (–)-terpestacin and the bond targeted for construction by metallacycle-mediated cross-coupling:

● = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.
● = bonds targeted for metallacycle-mediated carbonyl insertion.

B. Alkyne–alkene coupling in Jamison's total synthesis of (–)-terpestacin:

Figure 39.
Total synthesis of (–)-terpestacin.

A. Structure of (9*S*,13*E*,15*E*)-deoxy-J₁-phytoprostane and the bonds targeted for construction by metallacycle-mediated cross-coupling:

— = bond targeted for metallacycle-mediated alkyne–alkene cross-coupling.
- - = bonds targeted for metallacycle-mediated carbonyl insertion.

B. Alkyne–alkene coupling in Mueller's total synthesis of (9*S*,13*E*,15*E*)-deoxy-J₁-phytoprostane:

Figure 40.
Total synthesis of deoxy-J₁-phytoprostanes

A. Structure of axinellamine A and B and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Alkyne–alkene coupling in Baran's total synthesis of axinellamines A and B:

Figure 41.
Total synthesis of axinellamines A and B.

A. General depiction of metal-mediated [2+2+2] annulation: **B. Mechanistic hypotheses regarding incorporation of the third coupling partner:** **C. Most applications of cross-coupling are bimolecular rather than trimolecular:**

Figure 42.
Introduction to metallacycle-mediated cross-coupling by $[2+2+2]$.

A. Structure of estrone and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Intermolecular [2+2+2] in Vollhardt's total synthesis of estrone:

Figure 43.
Total synthesis of estrone.

A. Structure of the protoberberine nucleus and the bonds targeted for construction by metallacycle-mediated cross-coupling:

↘ = bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Vollhardt's synthesis of the protoberberine nucleus:

Figure 44.
Synthesis of the protoberberine nucleus.

A. Structure of sporolide B and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Intermolecular [2+2+2] in Nicolaou's synthesis of the sporolide B:

Figure 45.
Total synthesis of sporolide B.

A. Structure of alcyopterosin A and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Intermolecular [2+2+2] in Sato's synthesis of the alcyopterosin A:

C. Proposed mechanistic course of the metallacycle-mediated annulation:

Figure 46.
Total synthesis of alcyopterosin A.

A. Structure of hyellazole and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Witulski's synthesis of the hyellazole:

Figure 47.
Total synthesis of hyellazole.

A. Structure of vitamin B₆ and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Interolecular [2+2+2] in Vollhardt's synthesis of the vitamin B₆:

Figure 48.
Total synthesis of vitamin B₆.

A. Structure of lysergene and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Vollhardt's synthesis of the lysergene:

Figure 49.
Total synthesis of lysergene.

A. Structure of lavendamycin and the bonds targeted for construction by metallacycle-mediated cross-coupling:

— = bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Nissen's synthesis of lavendamycin:

Figure 50.
Total synthesis of lavendamycin methyl ester.

A. Structure of (+)-complanadine A and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Intermolecular [2+2+2] in Siegel's synthesis of (+)-complanadine A:

Figure 51.
Total synthesis of (+)-complanadine A.

Figure 52.
Co-catalyzed [2+2+2] of isocyanatoalkynes with TMS-alkynes.

A. Structure of camptothecin and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Vollhardt's formal synthesis of camptothecin:

Figure 53.
Formal total synthesis of camptothecin.

Rovis' metallacycle-mediated alkenyl isocyanate–alkyne [2+2+2] cycloaddition:

proposed mechanism:

Figure 54.
Rh-catalyzed alkenyl isocyanate – alkyne [2+2+2].

A. Structure of (+)-lasubine II and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Rovis' total synthesis of (+)-lasubine II:

Figure 55.
Total synthesis of (+)-lasubine II.

A. Structure of alkaloid (–)-209D and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Intermolecular [2+2+2] in Rovis' total synthesis of alkaloid (–)-209D:

Figure 56.
Total synthesis of alkaloid (–)-209D.

Figure 57.
Metallacycle-mediated cross-coupling between enynes and an alkyne by [2+2+2] annulation.

A. Structure of γ -lycorane and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Vollhardt's formal total synthesis of γ -lycorane:

Figure 58.
Total synthesis of γ -lycorane.

A. Structure of strychnine and the bonds targeted for construction by metallacycle-mediated cross-coupling:

= bonds targeted for metallacycle-mediated [2+2+2].

B. Intermolecular [2+2+2] in Vollhardt's formal total synthesis of strychnine:

Figure 59.
Formal total synthesis of strychnine.

A. Structure of (2*S*)-hydroxy-3,4-dehydroneomajucin and the bonds targeted for construction by metallacycle-mediated cross-coupling:

B. Intermolecular [2+2+2] in Micalizio's total synthesis of (2*S*)-hydroxy-3,4-dehydroneomajucin:

Figure 60.

Total synthesis of (2*S*)-hydroxy-3,4-dehydroneomajucin.

A. Structure of (–)-kainic acid, (+)-α-alkokainic acid and isodomoic acids H and G:

B. Montgomery's intramolecular Ni-catalyzed cyclization and intermolecular coupling in the total synthesis of kainoid natural products:

Figure 61.

Total synthesis of kainoids by sequential Ni-catalyzed cyclization and intermolecular coupling.

A. Structure of carbacyclin and the bonds targeted for construction in a complex metallacycle-mediated cyclization and intermolecular aldol:

• = bond targeted for construction post metallacycle-formation.

— = bond targeted for construction post-metallacycle formation.
 — = bond targeted for intramolecular metallacycle-forming process.

B. Sato's Ti-mediated annulation and coupling process for the total synthesis of carbacyclin:

Figure 62.
Total synthesis of (+/-)-carbacyclin.

Figure 63.

Whitby's application of allylic carbenoid species to convert zirconacyclopentanes to ring-expanded allylzirconiums.

A. Structure of 9-hydroxysargaquinone and the bonds targeted for construction in Whitby's Zr-centered multi-component coupling reaction:

↘ = bonds targeted for construction in the multi-component metallacycle-centered coupling reaction.

B. Whitby's Zr-mediated multi-component coupling reaction in the total synthesis of 9-hydroxysargaquinone:

Figure 64.
Synthesis of 9-hydroxysargaquinone.

A. Structure of acetoxydontoschismenol and the bonds targeted for construction in Whitby's Zr-centered multi-component coupling reaction:

• = bonds targeted for construction in the multi-component metallacycle-centered coupling reaction.

B. Whitby's Zr-mediated multi-component coupling reaction in the total synthesis of (+/-)-acetoxydontoschismenol:

Figure 65.
Synthesis of (+/-)-acetoxydontoschismenol.

Figure 66.

Hoveyda's Zr-catalyzed regio- and stereoselective carbomagnesiation.

A. Structure of fluvirucin B₁ and the bonds targeted for construction by metallacycle-mediated cross-coupling:

↘ = bonds targeted for construction by metallacycle-mediated cross-coupling and functionalization.

B. Use of metallacycle-mediated cross-coupling in Hoveyda's synthesis of fluvirucin B₁:

Figure 67.
Synthesis of fluvirucin B₁.

A. Structure of (+)-spirolaxine methyl ether and the bond targeted for construction by metallacycle-mediated cross-coupling:

= bond targeted for construction by metallacycle-mediated cross-coupling.

B. Use of metallacycle-mediated cross-coupling in Phillips' synthesis of (+)-spirolaxine methyl ether:

Figure 68.
Synthesis of (+)-spirolaxine methyl ether.

A. Structure of demethyl (C-11) cezomycin and the bond targeted for construction by metallacycle-mediated cross-coupling:

= bond targeted for construction by metallacycle-mediated cross-coupling.

B. Use of metallacycle-mediated cross-coupling in Wu's synthesis of demethyl (C-11) cezomycin:

Figure 69.
Synthesis of dimethyl (C-11) cezomycin.