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The Development of Alkoxide-Directed Metallacycle-Mediated Annulative Cross-Coupling Chemistry

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Abstract

Alkoxide-directed metallacycle-mediated cross-coupling is a rapidly growing area of reaction methodology in organic chemistry. Over the last decade, developments have resulted in > thirty new and highly selective intermolecular (or “convergent”) C–C bond-forming reactions that have established powerful retrosynthetic relationships in stereoselective synthesis. While early studies were focused on developing transformations that forge a single C–C bond by way of a functionalized and unsaturated metallacyclopentane intermediate, recent advances mark the ability to employ this organometallic intermediate in additional stereoselective transformations. Among these more advanced coupling processes, those that embrace the metallacycle in subsequent [4+2] chemistry have resulted in the realization of a number of highly selective annulative cross-coupling reactions that deliver densely functionalized and angularly substituted carbocycles. This review discusses the early development of this chemistry, recent advances in reaction methodology, and shares a glimpse of the power of these processes in natural product synthesis.

Keywords

metallacycle-mediated cross-coupling; [2+2+2] annulation; titanium; directed reaction; carbocycle synthesis

1. Introduction

Convergent carbon–carbon (C–C) bond formation is a cornerstone of organic synthesis. Reaction methods that enable union of organic molecules through the selective formation of one, or multiple, C–C bonds are critically important for complex molecule synthesis and are therefore of great significance to neighbouring disciplines where the products of organic synthesis can play a prominent role (i.e. biology and medicine). Among the variety of methods available for highly selective intermolecular C–C bond formation, those that proceed in an annulative manner have additional relevance in complex molecule synthesis.^[1] In such processes intermolecular union is accompanied by the formation of at least one ring, and therefore must proceed by the generation of at least two new bonds (σ - and/or π).^[2] Classic examples of annulative coupling technology include intermolecular cycloaddition (i.e. [4+2], [3+2], [2+1], and non-concerted variants), tandem nucleophilic addition to

polarized π -bonds (i.e. the Robinson annulation), and radical cascade reactions, among others.^[1] Standing alongside these, and offering complementary retrosynthetic relationships, is metallacycle-mediated annulative coupling technology (Figure 1A). Here, metal-centered [2+2+1] chemistry first delivers an unsaturated metallacyclopentane that can participate in subsequent ring-forming processes.^[3] Examples of such include the Reppe reaction,^[4] where alkyne trimerization results in the formation of benzenes, and the Pauson–Khand reaction,^[5] where cyclopentenones are generated from the union of an alkyne with an alkene and CO (Figure 1B). Despite the now commonly accepted power of these metallacycle-mediated annulative coupling reactions in organic synthesis, they both remain quite limited in scope. In fact, intermolecular variants are typically constrained to minimally substituted/unhindered species and/or the use of at least one symmetric coupling partner to avoid challenges with controlling regioselectivity.^[6,7] These facts speak to the broad limitations of metallacycle-mediated annulative crosscoupling chemistry, including challenges associated with: (1) favouring cross-coupling over homocoupling, (2) sensitivity to non-bonded steric interactions, (3) regioselectivity when employing unsymmetrical coupling partners, (4) stereoselectivity, and (5) functional group compatibility (Figure 1C).

In 2003 we established a program aimed at revolutionizing metallacycle-mediated cross-coupling chemistry.^[8] We believed that unaddressed issues associated with control of reactivity and selectivity had relegated this broad area of chemistry to a stage of infancy. This perspective fuelled our interest in charting a new course for the area, one that would be defined by providing solutions to problems associated with controlling metal-centered [2+2+1] chemistry, independent of the nature and stoichiometry of the metal employed. As a laboratory that is heavily engaged in organic synthesis, we moved forward with a search for straightforward solutions that would, above all else, provide new retrosynthetic relationships of relevance to complex molecule synthesis while delivering methods that are functional group tolerant, user friendly (i.e. no glove box required), and inexpensive (i.e. no rare metals or exotic ligands).

In addition to the discovery of now over thirty stereoselective metallacycle-mediated cross-coupling reactions, our efforts have resulted in the discovery of a suite of annulation methods for the union of internal alkynes with enynes. These reaction methods deliver a variety of highly substituted and stereodefined carbocycles in a concise and convergent manner. Here, we provide a *Perspective* on our discovery, development, and exploration of these amazing annulation methods that forge angularly substituted *cis*- and *trans*-fused hydrindane and decalin systems in a convergent and highly selective fashion.

2. Hydroxyl Directed Metallacycle-Mediated Cross-Coupling

2.1. Background

Being students of organic synthesis, we envisioned a general means to control metallacycle-mediated cross-coupling by rendering the area of reactivity “directed.” Directed reactions have long been recognized as among the most selective and useful transformations in organic chemistry, albeit the most frequently employed of these forge carbon–hydrogen or carbon–heteroatom bonds.^[10] Given our great interest in developing methods that could simplify synthesis strategies toward complex natural product and natural product-like agents,

we aimed to direct metallacycle-mediated coupling with functional groups that are commonplace in such pursuits. As such, we settled on free hydroxyls as the directing group of choice – these ubiquitous functional groups are often undesirable spectators in numerous key steps of complex molecule construction, typically being masked with protecting groups in order to execute chemical transformations at other molecular sites.^[11]

Our perspective regarding methods development in this area led to the natural identification of $\text{Ti}(\text{OR})_4$ -based metallacycle-mediated coupling chemistry as an ideal candidate for development. Titanium alkoxides are known to undergo rapid and reversible ligand exchange with hydroxylated substrates, a behaviour that is central to the control of the Sharpless epoxidation.^[12] In the early 2000's, we appreciated that metallacycle-based reaction methods had been evolving from Kulinkovich's discovery of a $\text{Ti}(\text{O}i\text{-Pr})_4$ -mediated hydroxycyclopropanation reaction. In this process, it has been proposed that a $(i\text{-PrO})_2\text{Ti}$ -alkene complex (Figure 2A) is the central organometallic intermediate that, when exposed to an ester, results in the formation of two C–C bonds and the establishment of a hydroxycyclopropane.^[13] These early findings were followed by those of Professors Fumie Sato and Jin Cha that demonstrated the reactive intermediate in the Kulinkovich reaction can be used as a reagent to generate new Ti–alkene and Ti–alkyne complexes of relevance for distinct reactions in organic chemistry.^[14]

We thought it reasonable that metal alkoxide-based ligand exchange at a preformed Ti–alkyne or Ti–alkene complex could render metallacycle-mediated coupling reactions alkoxide-directed.^[8] While one such generic process is depicted in Figure 2B, we imagined that at a number of related reaction designs may be effective for controlling untold numbers of new metallacycle-mediated cross-coupling reactions with simple unsaturated alcohols.

Reviews have already appeared that summarize our development of alkoxide-directed metallacycle-mediated cross-coupling chemistry that has grown from several different designs.^[8] Here, focus is given to efforts that have resulted in discovery of the most complex metallacycle-mediated annulative cross-coupling reactions ever described, and a collection of methods are summarized that afford concise stereoselective pathways for the synthesis of densely functionalized fused carbocycles.

2.2. Cross-Coupling Between Internal Alkynes

In January of 2005, Jamie Ryan demonstrated that the simple reaction design illustrated in Figure 2B could control the course of a metallacycle-mediated cross-coupling reaction.^[15] These early studies were focused on the challenging reductive cross-coupling of two internal alkynes. While examples of related metallacycle-mediated coupling with at least one terminal alkyne had been known for some time, the reductive cross-coupling of two internal alkynes remained a significant challenge.^[8a, 8b]

Her first success in this area was the coupling of diphenylacetylene (**7**) with 3-pentyne-1-ol (**8**) (Figure 3A). Following the generation of a Ti–alkyne complex (alkyne + $\text{ClTi}(\text{O}i\text{-Pr})_3$ + 2 $c\text{-C}_5\text{H}_9\text{MgCl}$), the second internal alkyne substrate was introduced as its corresponding Li-alkoxide. After warming from -78 to -30 °C, quenching of the reaction with a saturated aqueous solution of NH_4Cl delivered a tetrasubstituted 1,3-diene-containing product (**9**) of a

highly regioselective reductive cross-coupling reaction (rs = 42:1). Control experiments then verified the essential nature of the metal alkoxide in promoting the coupling process – substrates lacking a homopropargylic or bis-homopropargylic alkoxide (**10–12**) were incapable of undergoing efficient coupling with diphenylacetylene.

While this initial success was exciting, it represented a cross-coupling process of only modest complexity, as regioselectivity was relevant in functionalization of just one of the substrates (**8**). We quickly focused our attention on the regioselective cross-coupling of two different unsymmetric reaction partners. To our great delight, it was soon found that such coupling processes could occur in a highly regioselective fashion.

As illustrated in Figure 3B, the reaction between **13** and **14** delivered a single product of cross-coupling (**15**) where the net carbometalation of each alkyne proceeded in a highly selective manner. Site-selective functionalization of **13** derives from the directed nature of the process (C–C bond formation distal to the hydroxyl group), while regioselective coupling of **14** is based on minimization of non-bonded steric interactions in the transition state (C–C bond formation occurs distal to the propargylic branch).

2.3. Alkene–Alkyne Cross-Coupling

Shortly after Jamie's success with the hydroxyl-directed alkyne–alkyne coupling process, we began pursuit of a much more challenging problem in organometallic chemistry — the regio- and stereoselective alkene–alkyne cross-coupling. We appreciated that site- and stereoselective carbometalation of internal, unpolarized and unstrained alkenes is particularly challenging with any organometallic reagent, and were aware of the impressive contributions of Professor Trost in the area of Ru-catalyzed Alder-ene chemistry.^[8c, 9] With this perspective and knowledge regarding the great limitations associated with all known chemical methods that proceed by addition of an intermediate organometallic species to an unpolarized and substituted alkene, we moved forward to explore the potential of hydroxyl-direction as a strategy to control metallacycle-mediated alkene–alkyne coupling.

By the Summer of 2005, Holly Reichard had demonstrated that our strategy for titanium-mediated hydroxyl-directed metallacycle-mediated cross-coupling was effective for the union of a symmetrical alkyne with a homoallylic alcohol.^[16] As illustrated in Figure 4A, this initial experiment mirrored our investigation of the alkyne–alkyne coupling, featuring the use of diphenylacetylene and a simple homoallylic alcohol (**16**). We were delighted to find that this coupling process proceeded again with exquisite selectivity, and delivered a single cross-coupled product (**17**) in 66% yield. As encountered in the alkyne–alkyne coupling, and consistent with our model for alkoxide-directed metallacycle-mediated cross-coupling (Figure 2B), C–C bond formation occurred distal to the directing group; here, proximal to the ethyl rather than the hydroxy ethyl substituent of **16**.

With our goal focused on establishing reaction methods of utility in organic synthesis, we quickly began exploration of more complex fragment union processes in this class of metallacycle-mediated cross-coupling. Illustrated in Figure 4B is one such case that demonstrates the ability to control regioselectivity with respect to both π -systems as well as diastereoselectivity.^[17] Here, union of the stereodefined homoallylic alcohol **19** with the

functionalized alkyne **20** resulted in the formation of **21** in 54% yield with no evidence found for regio- or stereoisomeric products.

2.4. Discovery of a Stereoselective Annulation Method

Our interests in reaction development have been firmly rooted in a desire to establish methods that have a significant impact on the efficiency with which complex molecules can be prepared. Naturally following from this desire, we were interested in exploring chemoselectivity^[18] in this emerging class of reactivity. In short, we sought to understand the factors that govern selectivity in reactions of polyunsaturated substrates. While these studies led to our finding of impressive selectivity as a function of substrate substitution, the most exciting discovery occurred in 2010 when we recognized that reaction between an internal alkyne and a 1,6-enyne containing a 1,1-disubstituted alkene delivered an angularly substituted hydrindane with exquisite levels of stereoselectivity (Figure 5A).^[19]

This complex coupling process, formally a [2+2+2] annulation, was the first of its kind. It establishes three new C–C bonds and one quaternary center with exquisite levels of stereoselection (20:1). Because the enyne substrates for this annulative cross-coupling can be readily prepared from epichlorohydrin (2–3 steps), a starting material that is accessible in either enantiopure form, this annulation defines the final step in a concise synthesis pathway to enantiodefined, densely functionalized and angularly substituted hydrindanes.

To address synthetic utility, as we have done earlier, we investigated this annulative cross-coupling process with two unsymmetrical reaction partners. As illustrated in Figure 5B, use of a TMS-alkyne as one of the coupling partners results in an annulation process that delivers an angularly substituted hydrindane possessing C11-silyl and C9-alkyl substituents (steroid numbering).

Our early studies of this annulation reaction included exploration of the mechanism by Stephen Greszler and led to the conclusion that the sequence of bond-forming events is likely initial regioselective alkoxide-directed alkyne–alkyne coupling to generate a metallacyclopentadiene (**27** + **28** → **29**), then stereoselective intramolecular [4+2] cycloaddition to furnish a bridged bicyclic metallacyclopentene (**29** → **30** → **31** → **32**), and finally cheletropic loss of the metal and generation of a cyclohexadiene (**32** → **33**; Figure 6). This final step of the process has been the subject of recent study, and it has been found that addition of a sacrificial π -system (i.e. PhCHO) better facilitates cheletropic loss of Ti from **32** without being complicated by potential protonation of the metastable organometallic intermediate (*vide infra*).

2.5. Convergent Synthesis of *trans*-Fused and Angularly Substituted Hydrindanes

Given the proposed mechanistic course of the annulation, involving intramolecular [4+2] rather than alkene insertion and reductive elimination, we speculated that it might be possible to direct the penultimate bridged bicyclic organometallic intermediate to engage in additional chemistry. The first attempt in this vein was to trap this intermediate through an elimination reaction (Figure 7A; **34** → **35**).^[20] The resulting tertiary allylic titanium intermediate (**35**) was expected to isomerize to a primary allylic metal species (**36**) which

could then be employed in regio- and stereoselective protonation *en route* to **37**. If possible, this variation of the annulation would deliver hydrindanes with two sp^3 carbons at the ring fusion, by way of a reaction that would forge three C–C bonds, one C–H bond, and two sp^3 stereocenters (one of which being quaternary).

In the early phases of our investigation of this more complex coupling process, we quickly directed attention to varying the reaction conditions employed in the basic annulation process. Moving away from ethereal solutions of Grignard reagents for the initial formation of a Ti–alkyne complex, due in part to the limitations that this procedure presents with regard to reaction concentration and the requirement of careful temperature control, Valer Jeso was delighted to find that *n*-BuLi in hexanes was particularly effective in these processes, allowing for the annulation reaction to proceed in a wholly hydrocarbon solvent system (toluene/hexanes) and without Mg-salts. Moving forward with the study, we found that enynes possessing a terminal propargylic ether (**39**; Figure 7B) were competent substrates for alkyne–alkyne coupling and intramolecular [4+2] cycloaddition. As expected, after cycloaddition the presumed bridged bicyclic metallacyclopentene promptly underwent an elimination reaction to generate a reactive allylic organometallic species that was amenable to regio- and stereoselective protonation. In all cases where the C9 substituent (steroid numbering) was branched, good levels of selectivity were observed favoring the angularly substituted and *trans*-fused hydrindane product (**40**).^[21]

This observation is noteworthy, as the establishment of *trans*-fused hydrindanes is well-appreciated to be challenging. Unlike the related *trans*-decalin system, *trans*-hydrindanes are typically less stable than their *cis*-fused stereoisomers and are not readily accessible from Birch reduction of bicyclic enones (i.e. substrates derived from Robinson annulation).

As with all reactions in organic chemistry, this annulation method was found to have limitations (i.e. variations in stereo- and regioselectivity in the final protonation) but it accomplishes a bimolecular union that is without precedent. It establishes stereodefined *trans*-fused and angularly substituted hydrindanes in a single step from acyclic precursors.

We have envisioned an empirical model that supports the stereochemical course of this process. As illustrated in Figure 8, we focus attention on the complex penultimate organometallic species in the cascade. This fused bicyclic carbocycle is quite rigid, projecting the C9 substituent above the plane of the allylic titanium moiety. Given the hindered rotation of the group at C9 due to the presence of the C11 trimethylsilyl group, we speculate that the electron density from the C9 substituent leads to conformational biasing of the allylic titanium during the transition state for protonation. To avoid non-bonded steric interactions between the C9 substituent and the ligated titanium atom in the transition state, positioning of the titanium center on the α -face of the system (as in **A**) and protonation by a *syn* S_E' mechanism is consistent with the observed preference for formation of *trans*-fused hydrindane products. This model is also consistent with the lower levels of *trans*-selectivity that we observed in the annulation employing smaller, unbranched substituents at the C9 position.

2.6. Convergent Synthesis of *cis*-Fused and Angularly Substituted Hydrindanes

Having a stereoselective pathway to *trans*-fused hydrindanes in hand, we hoped to broaden the utility of this chemistry by developing a stereodivergent pathway for selective generation of *cis*-fused hydrindanes. In fact, both *cis*- and *trans*-fused hydrindanes are ubiquitous motifs in natural products.

To accomplish this, we speculated that a carbocyclic allylic alcohol may be an ideal candidate for stereoselective reductive transposition chemistry (**41** → **42**; Figure 9A). Unfortunately, the allylic alcohol substrate for such a proposed reductive transposition (**41**) would not be readily available from our annulation method, as heteroatom functionality at the required position of the enyne starting material results in an organometallic intermediate that we have previously exploited in elimination chemistry *en route* to an allylic titanium species (see section 2.5).

To access functionalized allylic alcohols like **41**, we decided to explore if the presumed penultimate organometallic species in the cascade reaction (a complex allylic titanium species) could be regioselectively oxidized. As depicted in Figure 9B, it was found that oxidation could be realized by quenching the annulation process with LiOO*t*-Bu.^[22] In contrast to the protonation experiments previously described, where the major product was formed from functionalization at the ring fusion, this oxidation selectively functionalizes the primary carbon of the system and leads to the desired allylic alcohol isomer.

Next, we explored the use of IPNBSH^[23] in the desired reductive transposition chemistry. To our delight, it was found that this reduction delivers *cis*-hydrindanes with good selectivity and without being significantly impacted by the structure of the C9 substituent (typically, *ds* ~ 6:1). In comparison to our annulation reaction for the preparation of *trans*-fused hydrindanes, here, the much smaller nature of the diazene motif in comparison to the allylic titanium species (i.e. Figure 8) results in progression through a path that preferentially delivers the more stable *cis*-fused hydrindane.

2.7. Convergent Synthesis of Decalins by Annulative Cross-Coupling and Discovery of a Stereoselective Protic Quench of Bridged Bicyclic Organotitaniums

Given the vast number of natural products and molecules of pharmaceutical relevance that contain fused six-membered rings, we aimed to explore the potential utility of this growing class of annulative cross-coupling reactions to the synthesis of angularly substituted decalins. While success in these endeavors required enyne substrates that were conformationally biased to support the transition state for intramolecular [4+2] cycloaddition (**47** + **48** → **49**; Figure 10),^[24] our pursuits led to an interesting discovery regarding the reactivity of bridged bicyclic metallacyclopentenes (i.e. **49**).

Through careful study, Haruki Mizoguchi found that ligand-induced cheletropic extrusion was the best means to promote the conversion of **49** to cyclohexadiene-containing products (**50**). Most interestingly, simple protic quenching of **49** led to the discovery of reaction processes that proceed through site- and stereoselective protonation of the complex organometallic intermediate. As illustrated in Figure 10, low temperature quenching with MeOH led to the *cis*-fused product **51** in 64% yield (*ds* ~ 20:1), while quenching with an

aqueous solution of NH_4Cl at 0°C produced tricycle **52**, a structure presenting both the TMS group and the *p*-methoxyphenyl substituent on the β -face of the molecule (ds = 20:1). To our knowledge, this site- and stereoselective reductive termination of a metal-centered [2+2+2] annulation is unique to these alkoxide-directed Ti-mediated coupling reactions. While exciting, the selectivity of these protonation processes remains poorly understood.

2.8. Convergent Synthesis of *trans*-Fused and Angularly Substituted Decalins

Given our experience with developing an annulation method for the synthesis of *trans*-fused hydrindanes, where termination of the coupling process proceeds through elimination and site- and stereoselective protonation, we wondered whether a similar cascade of transformations could be employed to deliver *trans*-fused decalins. While seemingly a minor modification of annulation chemistry that we previously secured, our pursuits here continue to deliver unexpected results and exciting findings.

Our initial effort was focused on the coupling of TMS-phenyl acetylene (**53**) with enyne **54** (Figure 11A). Employing similar reaction conditions to those used for the annulative cross-coupling that generated *trans*-fused hydrindanes, we were surprised to find that the major product here was the endocyclic diene-containing tricycle **56** where protonation of the presumed allylic titanium species did not proceed with the desired sense of regioselection. The *trans*-fused tricycle **57** was produced as the minor product of a 3:1 mixture of tricycles (no evidence was found for the presence of the *cis*-isomer).

This observation regarding regioselectivity in the final protonation was surprising and remains not well understood. That said, we appreciated that it was possible that the allylic titanium species has the potential to undergo rapid and reversible 1,3-isomerization, and that the protonation could proceed by a number of different mechanistic courses (direct protonation of the $\sigma_{\text{C-Ti}}$ vs S_E' -based protonation). Without a firm understanding of the source of the observed difference in selectivity for protonation here, we speculated that the benzylic alkoxide in intermediate **55** has the potential to coordinate to the tertiary allylic titanium isomer and stabilize the unwanted intermediate for S_E' -protonation (*not shown*). To perturb its propensity to engage in such a coordination event, we pursued silylation of the alkoxide prior to protic quench. Delightfully, when we intervened with the addition of TMSCl prior to the protic quench,^[25] a substantial shift in selectivity was observed.^[26] As illustrated in Figure 11B, this modification to the reaction procedure produced the *trans*-fused product containing a benzylic TMS-ether (**58**) in 69% yield. Here, not only was the stereoselectivity of the process quite high (20:1), no evidence was found for the production of a regioisomeric product.

Consistent with our past experiences in this exciting area of chemistry, we next found that subtle structural changes on the enyne result in substantial perturbations in selectivity. As demonstrated in Figure 11C, substrates containing an *o*-TMS group delivered the *cis*-fused decalins **60** and **62** as the major product (ds = 3:1, 14:1 respectively), where the benzylic alcohol was found to be unsilylated (presumably the alkoxide intermediate is much more sterically hindered than the benzylic alkoxide of **55**).

Despite the apparent sensitivity of this annulative coupling process to minor structural changes of the substrates employed, we are looking enthusiastically to the future development of this interesting area of reactivity.

2.9. Application of Metallacycle-Mediated Annulative Cross-Coupling Reactions in Natural Product Synthesis

The development of alkoxide-directed metallacycle-mediated annulative cross-coupling technology has only just begun, with our enthusiasm for the potential power of this class of reaction growing daily. Our laboratory has initiated efforts to explore the potential significance of these annulation methods in natural product synthesis and has recently reported our first successes in such pursuits.^[27]

As illustrated in Figure 12A, our first-generation annulation for the synthesis of angularly substituted hydrindanes played a central role in our approach to the assembly of the pentacyclic core of the cortistatins (**63** + **64** → **65** → **67**).

We have also employed this annulation in three total syntheses of members of the neurotrophic *seco*-prezizaane family of natural products. As illustrated in Figure 12B, these efforts proceeded by way of a unique variation of the annulation reaction. Regioselective coupling was achieved with 1-tributylstannyl-2-trimethylsilyl-acetylene (**69**), and delivered the complex hydrindane **70** in 73% yield as a single isomer. Six additional steps that included a radical cyclization process delivered the densely functionalized tricycle **71** that was eventually converted to three different members of this natural product class, including (*1R,10S*)-2-oxo-3,4-dehydroneomajucin (**72**).

3. Summary and Outlook

Our program has had as its major focus the desire to discover, invent, and develop reaction methods and synthesis strategies that have the potential to impact the efficiency with which complex molecules can be prepared. It is with such contributions that we believe lasting impact can be made at the core of organic chemistry and the neighbouring disciplines that thrive as a result of the properties of molecules prepared through organic synthesis. We first focused our attention on identifying the great value of convergent C–C bond formation in natural product synthesis, and then came to the conclusion that few general reaction strategies are routinely embraced for such a valuable class of fragment union processes. We next moved boldly in a direction to conceive of a type of reactivity that may be particularly powerful as an entry to new coupling technology and the establishment of fundamentally novel retrosynthetic relationships. This line of inquiry, and our appreciation of the great role that π -unsaturated architecture plays in modern chemical synthesis, led us to propose that if one could control the basic reactivity central to metallacycle-mediated cross-coupling that it would be possible to conceive of a myriad of new coupling methods. This yearning, and the desire to invent practical methods that do not require glovebox techniques and expensive metal promoters/catalysts and/or ligands, as well as having the goal of achieving hydroxyl-directed cross-coupling technology, ultimately led us to pursue reaction development that embraced the intermediacy of titanium alkoxide-centered metallacycles. This began a journey that has led to the development of more than thirty new synthetic methods where

metallacycle-mediated coupling takes center stage. Among these advances are the annulative methods that are the topic of this *Perspective*. In pursuits that have blossomed from our general interest in controlling the course of basic organometallic chemistry we find ourselves on fertile ground for additional discovery. These annulation methods are, in our opinion, among the most complex intermolecular [2+2+2] processes known, and deliver convenient access to densely functionalized carbocyclic motifs found in many natural products and molecules of biomedical relevance. As with all new synthetic methods, their value to our field remains speculative, with only a handful of natural product synthesis efforts that have benefitted from these processes to date. While we continue to explore the application of annulative cross-coupling chemistry in target-oriented pursuits, investigate the factors that impact reactivity and selectivity for these processes, and conceive of ever more complex cascade reactions in this area, we look forward to ushering in many new metallacycle-mediated convergent coupling reactions to the lexicon of powerful methods for organic synthesis.

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Biographies

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.

Haruki Mizoguchi received his PhD at Hokkaido University (2013) after graduate studies in the laboratory of Professor Hideaki Oikawa and Professor Hiroki Oguri. After postdoctoral training at the same university (2013), he joined to the laboratory of Professor Micalizio at Dartmouth College as a fellow of the Uehara Memorial Foundation (2013), and most recently, as a fellow of the Japan Society for the Promotion of Science (JSPS Postdoctoral fellow for research abroad). His research interests are focused on the development of reaction methods and synthesis strategies that offer concise solutions to problems associated with the preparation of complex structural motifs relevant to biologically active molecules.

References

1. For reviews and selected examples of annulation chemistry, see: Kobayashi S, Jørgensen KA. Cycloaddition Reactions in Organic Synthesis. 2001 Weinheim Wiley-VCH Jung ME. Tetrahedron. 1976; 32:3–31. Gawley RE. Synthesis. 1976:777–794. Mal D, Pahari P. Chem. Rev. 2007; 107:1892–1918. [PubMed: 17444689] Danheiser RL, Carini DJ, Fink DM, Basak A. Tetrahedron. 1983; 39:935–947. Rheault TR, Sibi MP. Synthesis. 2003:803–819. Larock RC, Yum EK. J. Am. Chem. Soc. 1991; 113:6689–6690.
2. For a definition of annulations as ring-forming processes in which two molecular fragments are united with the formation of two new bonds, see: Danheiser RL, Gee SK, Sard H. J. Am. Chem. Soc. 1982; 104:7670–7672.
3. Micalizio, GC. Comprehensive Organic Synthesis. Molander, GA., Knochel, P., editors. Vol. 5. Oxford: Elsevier; 2014. p. 1660–1737.
4. Reppe W, Schweckendick WJ. Justus Liebigs Ann. Chem. 1948; 560:104–116.
5. For recent reviews, see: Brummond KM, Kent JL. Tetrahedron. 2000; 56:3263–3283. Boñaga LVR, Krafft ME. Tetrahedron. 2004; 60:9795–9833.
6. Gibson SE, Mainolfi N. Angew. Chem. Int. Ed. 2005; 44:3022–3037.
7. Agenet N, Buisine O, Slowinski F, Gandon V, Aubert C, Malacria M. Org. React. 2007; 68:1–302.
8. For reviews, see: (a) ref. 3 Reichard HA, McLaughlin M, Chen MZ, Micalizio GC. Eur. J. Org. Chem. 2010:391–409. Reichard HA, Micalizio GC. Chem. Sci. 2011; 2:573–589.
9. Trost BM, Frederiksen MU, Rudd MT. Angew. Chem. Int. Ed. 2005; 44:6630–6666.
10. For reviews, see: Hoveyda AH, Evans DA, Fu GC. Chem. Rev. 1993; 93:1307–1370. Breit B. Chem. Eur. J. 2000; 6:1519–1524. [PubMed: 10839167] Oestreich M. Eur. J. Org. Chem. 2005:783–792.
11. For early examples of hydroxyl-directed metallacycle-mediated cross-coupling, see: Takai K, Yamada M, Odaka H, Utimoto K. J. Org. Chem. 1994; 59:5852–5853. Takai K, Yamada M, Odaka H, Utimoto K, Fujii T, Furukawa I. Chem. Lett. 1995:315–316. For a perspective on the development of protecting-group-free syntheses, see: Young IS, Baran PS. Nature Chem. 2009; 1:193–205. [PubMed: 21378848]
12. Katsuki T, Martin VS. Org. React. 1996; 48:1–299.
13. (a) Kulinkovich OG, Sviridov SV, Fasilevski DA, Pritytskaya TS. J. Org. Chem. USSR (Eng. Transl.). 1989; 25:2027–2028. (b) Kulinkovich OG, Meijere A. Chem. Rev. 2000; 100:2789–2834. [PubMed: 11749306]
14. (a) Harada K, Urabe H, Sato F. Tetrahedron Lett. 1995; 36:3203–3206. (b) Kasatkin A, Nakagwa T, Okamoto S, Sato F. J. Am. Chem. Soc. 1995; 117:3881–3882. (c) Lee J, Kang CH, Kim H, Cha JK. J. Am. Chem. Soc. 1996; 118:291–292.
15. Ryan J, Micalizio GC. J. Am. Chem. Soc. 2006; 128:2764–2765. [PubMed: 16506731]

16. Reichard HA, Micalizio GC. *Angew. Chem. Int. Ed.* 2007; 46:1440–1443. Canterbury DP, Micalizio GC. *J. Am. Chem. Soc.* 2010; 132:7602–7604. [PubMed: 20476790] For other examples of hydroxyl-directed alkene–alkyne coupling, see: Kolundzic F, Micalizio GC. *J. Am. Chem. Soc.* 2007; 129:15112–15113. [PubMed: 18004854] Macklin TK, Micalizio GC. *Nat. Chem.* 2010; 2:638–643. [PubMed: 20651725] Diez PS, Micalizio GC. *J. Am. Chem. Soc.* 2010; 132:9576–9578. [PubMed: 20586460] Diez PS, Micalizio GC. *Angew. Chem. Int. Ed.* 2012; 51:5152–5156.
17. Hoffmann RW. *Chem. Rev.* 1989; 89:1841–1860.
18. Afagh NA, Yudin AK. *Angew. Chem. Int. Ed.* 2010; 49:262–310.
19. Greszler SN, Reichard HA, Micalizio GC. *J. Am. Chem. Soc.* 2012; 134:2766–2774. [PubMed: 22235773]
20. For examples that engage a proposed metallacyclopentene formed from [4+2] in an elimination process, see: Suzuki D, Urabe H, Sato F. *J. Am. Chem. Soc.* 2001; 123:7925–7926. [PubMed: 11493074] Tanaka R, Nakano Y, Suzuki D, Urabe H, Sato F. *J. Am. Chem. Soc.* 2002; 124:9682. [PubMed: 12175207] Suzuki D, Tanaka R, Urabe H, Sato F. *J. Am. Chem. Soc.* 2002; 2002:3518–3519. Tanaka R, Yuza A, Watai Y, Suzuki D, Takayama Y, Sato F, Urabe H. *J. Am. Chem. Soc.* 2005; 127:7774–7780. [PubMed: 15913367]
21. Jeso V, Aquino C, Cheng X, Mizoguchi H, Nakashige M, Micalizio GC. *J. Am. Chem. Soc.* 2014; 136:8209–8212. [PubMed: 24856045] For other recent approaches to establishing angularly substituted *trans*-fused hydrindanes, see: Ross AG, Li X, Danishefsky SJ. *J. Am. Chem. Soc.* 2012; 134:16080–16084. [PubMed: 22950514] Brusoe AT, Alexanian EJ. *Angew. Chem. Int. Ed.* 2011; 50:6596–6600. Wilson RM, Jen WS, MacMillan DWC. *J. Am. Chem. Soc.* 2005; 127:11616–11617. [PubMed: 16104734]
22. Kim WS, Aquino C, Mizoguchi H, Micalizio GC. *Tetrahedron Lett.* 2015; 56:3557–3559.
23. (a) Movassaghi M, Ahmad OK. *J. Org. Chem.* 2007; 72:1838–1841. [PubMed: 17274659] (b) Movassaghi M, Piizi G, Siegel DS, Piersanti G. *Angew. Chem. Int. Ed.* 2006; 45:5859–5863. (c) Myers AG, Zheng B, Movassaghi M. *J. Org. Chem.* 1997; 62:7507. [PubMed: 11671877]
24. Mizoguchi H, Micalizio GC. *J. Am. Chem. Soc.* 2015; 137:6624–6628. [PubMed: 25930967]
25. Cassidy JS, Mizoguchi H, Micalizio GC. *Tetrahedron Lett.* 2016; 57:3848–3850. [PubMed: 27713588]
26. Mizoguchi H, Micalizio GC. *Angew. Chem. Int. Ed.* 2016; 55 *accepted*;
27. (a) Aquino C, Greszler SN, Micalizio GC. *Org. Lett.* 2016; 18:2624–2627. [PubMed: 27193994] (b) Cheng X, Micalizio GC. *J. Am. Chem. Soc.* 2016; 138:1150–1153. [PubMed: 26785051]

A. General depiction of metal-centered annulative cross-coupling. **B. Examples.**Reppe reaction Pauson-Khand reaction **C. Challenges for this class of intermolecular chemistry.**

- Cross-coupling vs. homo-dimerization
- Sensitivity to non-bonded steric interactions
- Regioselectivity (with unsymmetric π -systems)
- Stereoselectivity
- Functional group compatibility

Figure 1.
Introduction.

A. The Kulinkovich reaction.

B. A hydroxyl-directed metallacycle-mediated cross-coupling.

Figure 2.

A focus on Ti(Oi-Pr)_4 for alkoxide-directed metallacycle-mediated cross-coupling.

A. A reductive cross-coupling between internal alkynes.

control experiments:

B. A hydroxyl-directed metallacycle-mediated cross-coupling.

Figure 3.
An alkoxide-directed alkyne–alkyne coupling.

A. An alkene–alkyne reductive cross-coupling. *control experiment:* **B. Control of regio- and stereoselection.**

Figure 4.
Alkoxide-directed alkene–alkyne coupling.

A. A stereoselective intermolecular [2+2+2] annulation. **B. Control of regio- and stereoselection.** **Figure 5.**

A complex and stereoselective metallacycle-mediated annulative cross-coupling.

Figure 6.
Proposed mechanism for the annulative cross-coupling.

A. A plan to access *cis*- or *trans*-fused hydrindanes by capturing the bridged bicyclic organometallic in the annulative cross-coupling.

B. *Trans*-fused angularly substituted hydrindanes by metallacycle-centered annulative cross-coupling.

Figure 7.

Annulative cross-coupling for the synthesis of angularly substituted *trans*-fused hydrindanes.

Figure 8.
An empirical model for the high levels of *trans*-selectivity observed in the annulative cross-coupling

A. Reduction of an allylic alcohol with allylic transposition - a potential pathway to *cis*-fused hydrindanes.

B. $\text{LiO}Ot\text{-Bu}$ as a terminal oxidant in the annulative cascade reaction.

a = TMS-phenylacetylene, $\text{Ti}(\text{O}i\text{-Pr})_4$, $n\text{-BuLi}$, PhMe; b = $\text{LiO}Ot\text{-Bu}$.

C. IPNBSh-mediated reduction is selective for *cis*-fused hydrindanes.

Figure 9.

A selective route to *cis*-fused hydrindanes.

Figure 10.
Decalin synthesis and unique pathways for quenching the penultimate organometallic intermediate.

**A. Targeting *trans*-decalins from annulative coupling/elimination/protonation:
Observation of unique regioselectivity in the protonation event.**

B. Effect of TMSCl on the regioselective protonation.

C. Stereoselectivity of terminal protonation is influenced by substrate structure.

Figure 11.
Annulative cross-coupling/elimination/protonation *en route* to *cis*- and *trans*-fused decalins.

A. Application to the pentacyclic core of the cortistatins. **B. Total syntheses of neurotrophic seco-prezizaane sesquiterpenes.** **Figure 12.**

Early applications in natural product synthesis efforts.