

Synthesis of Highly Functionalized Decalins via Metallacycle-Mediated Cross-Coupling

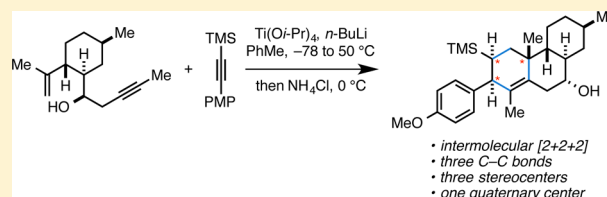
Haruki Mizoguchi and Glenn C. Micalizio*

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

S Supporting Information

ABSTRACT: Bridged bicyclic metallacyclopentenes generated from the [4 + 2] cycloaddition of metallacyclopentadienes with alkenes have been proposed as reactive intermediates in the course of [2 + 2 + 2] annulation reactions. Recently a collection of alkoxide-directed Ti-mediated [2 + 2 + 2] annulation reactions have been discovered for the synthesis of densely functionalized hydrindanes, where the bridged bicyclic metallacyclopentenes from intramolecular [4 + 2] were treated as fleeting intermediates

en route to cyclohexadiene products formed by formal cheletropic extrusion of $\text{Ti}(\text{O}i\text{-Pr})_2$. In studies aimed at understanding the course of these organometallic cascade reactions it was later discovered that these bridged bicyclic intermediates can be trapped by various elimination processes. Here, we have realized metallacycle-mediated annulation reactions for the assembly of angularly substituted decalins—structural motifs that are ubiquitous in natural products and molecules of pharmaceutical relevance. In addition to defining the basic annulation reaction we have discovered a surprising stability associated with the complex organometallic intermediates generated in the course of this coupling process and document here the ability to control the fate of such species. Ligand-induced cheletropic extrusion of the titanium center delivers cyclohexadiene-containing products, while several distinct protonation events have been identified to realize polycyclic products that contain three new stereocenters (one of which is the angular quaternary center that is a hallmark of alkoxide-directed titanium-mediated [2 + 2 + 2] annulation reactions). Examples of this metallacycle-mediated annulation reaction are provided to demonstrate that a range of stereodefined fused bicyclo[4.4.0]decanes are accessible, including those that contain aromatic and aliphatic substituents, and an empirical model is presented to accompany the observations made.



INTRODUCTION

Metal-centered [2 + 2 + 2] annulation is a powerful means to prepare complex carbocyclic skeletons found in numerous complex natural products and pharmaceutically relevant agents.^{1,2} Early examples include Co-mediated intramolecular cyclization reactions of enediyne (and related polyunsaturated species) that deliver polycyclic diene-containing products, often with excellent levels of stereoselectivity.³ While much progress has been made in developing this area of chemical reactivity, there remain substantial challenges that limit the great potential utility of this mode of reactivity to access pathways for the efficient synthesis of a range of carbocyclic targets. For example, while effective in wholly intramolecular settings, it is often the case that intermolecular variants are complicated by issues related to the control of regio- and stereoselectivity in various steps of the cascade process, thereby complicating the use of this reactivity for convergent synthesis. This situation is particularly relevant in the context of carbocyclic targets that contain angular substitution (a quaternary stereocenter at the ring fusion) and is therefore an issue that substantially limits the utility of [2 + 2 + 2] chemistry for the efficient assembly of terpene-derived targets.

Recently we reported a titanium alkoxide centered cascade reaction that defined a concise, convergent, and highly selective synthesis of angularly substituted hydrindanes from acyclic

precursors (Figure 1; 1 + 2 → 4).⁴ This process was proposed to proceed by initial alkoxide-directed metallacycle-mediated alkyne–alkyne coupling, followed by intramolecular [4 + 2] cycloaddition to generate the presumed bridged bicyclic metallacyclopentene intermediate 3. This species was then envisioned to undergo a formal cheletropic extrusion of $\text{Ti}(\text{O}i\text{-Pr})_2$ and produce the angularly substituted diene-containing hydrindane product 4. In later work, we realized a strategy to trap intermediate 3 by double elimination ($\text{Y} = \text{OMe}$, $\text{R}^1 = \text{CH}_2\text{OR}^5$) and, in so doing, secured a pathway to stereodefined angularly substituted hydrindanes possessing a highly reactive cross-conjugated triene (5).⁵ In other efforts, installation of an appropriately situated allylic ether in 3 (i.e., $\text{R}^1 = \text{CH}_2\text{OPh}$ or CH_2OPMB) led to rapid elimination and the formation of a transient allylic titanium species that could be protonated with site- and stereoselectivity. Products of this latter annulation process are *trans*-fused hydroindanes 6.⁶

While realizing a means to accomplish intermolecular variants of [2 + 2 + 2] chemistry that furnish angularly substituted hydrindanes with high levels of stereoselectivity was viewed as a significant success, this reactivity was observed only for annulation reactions that delivered hydrindanes, i.e. with

Received: March 5, 2015

Published: May 1, 2015

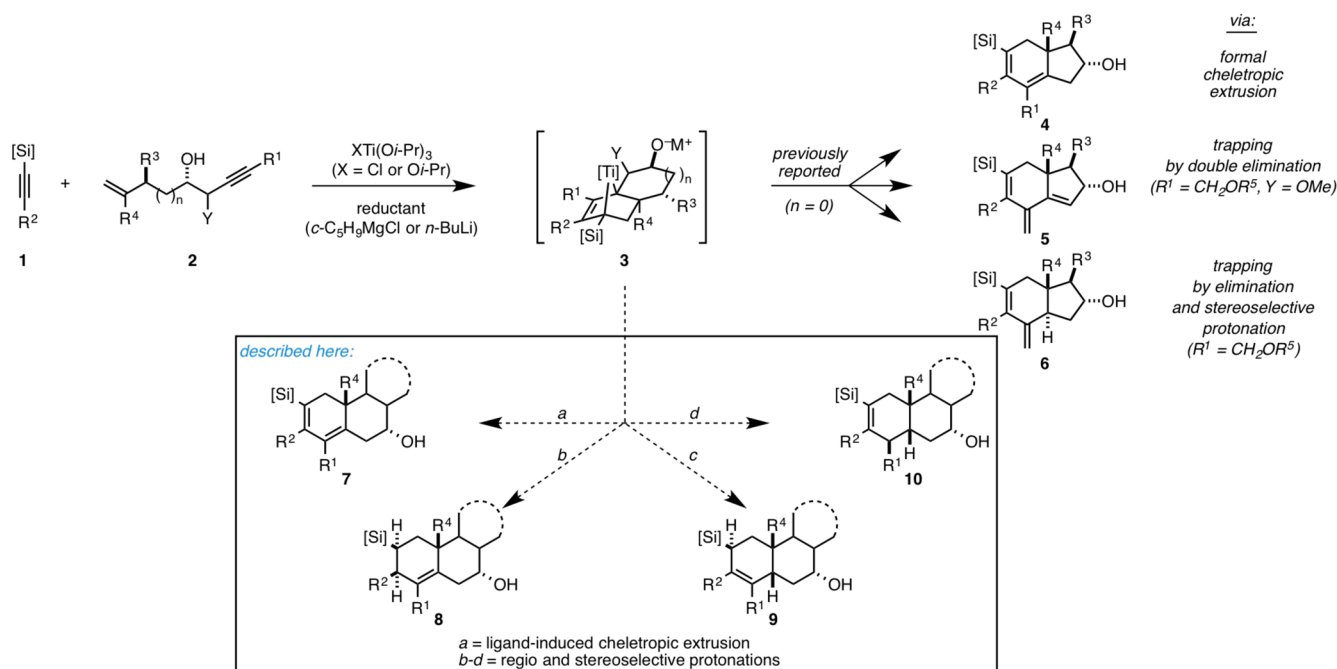


Figure 1. Titanium-centered intermolecular [2 + 2 + 2] chemistry by way of a polycyclic metallacyclopentene intermediate (3).

substrates that could, after alkoxide-directed alkyne–alkyne coupling,⁷ undergo intramolecular cycloaddition to form a five-membered ring. Also, while one could imagine a rich reactivity profile associated with the metallacyclopentene intermediate 3, we have been able to divert its reactivity away from standard cheletropic extrusion of $\text{Ti}(\text{O}i\text{-Pr})_2$ only by elimination pathways (en route to 5 or 6).^{5,6} Here, we report a substantial advance in this general area of chemical reactivity, defining a means to realize intermolecular alkoxide-directed titanium-centered [2 + 2 + 2] annulation chemistry for the synthesis of angularly substituted decalins, and discovering that the resulting metallacyclopentene intermediates formed on cycloaddition (3, $n = 1$) can progress down distinct reaction pathways en route to more stereochemically complex products. Our studies have resulted in convergent annulation reactions that can be terminated not only by ligand induced cheletropic extrusion (7) but also by site-selective and stereoselective protonation (8–10). These latter pathways define novel reaction cascades in the broader area of metal-centered [2 + 2 + 2] annulation and provide convenient access to densely functionalized and stereochemically rich decalin-containing polycycles.

RESULTS AND DISCUSSION

The present study began with an inquiry aimed at understanding the scope and limitations of titanium-centered alkoxide-directed metallacycle-mediated [2 + 2 + 2] annulation of TMS-alkynes with substituted enynes. With our goals focused on realizing a means to achieve annulation reactions for the synthesis of angularly substituted decalins, we began exploring the reactivity of enyne substrates in metallacycle-mediated coupling chemistry that have an increased tether length (the number of carbons between the two π -unsaturated units would be increased from three to four). Perhaps not surprisingly, our initial attempt in this vein was met with failure (Table 1, entry 1). Here, Ti-mediated union of enyne 11 with TMS-alkyne 12 did not deliver the angularly substituted decalin 13. Rather, on protonation of the presumed intermediate

organometallic species, the expected product of simple alkoxide-directed alkyne–alkyne coupling was observed (a tetrasubstituted 1,3-diene, not shown).⁷ This result is consistent with the conclusion that, while the alkyne–alkyne coupling remains effective for this substrate class, there exists a larger energetic barrier for intramolecular cycloaddition in comparison to that associated with the annulation processes previously achieved for the convergent synthesis of hydrindanes.^{4–6}

Recognizing that our failure to achieve the desired reactivity profile likely derives from a greater entropic penalty associated with intramolecular cycloaddition, we contemplated the use of substrates that are more conformationally predisposed to cyclization. The first experiment in this vein is depicted in entry 2 of Table 1 and is based on employing a tether that incorporates an *o*-disubstituted aromatic. Here, treatment of alkyne 12 with the combination of $\text{Ti}(\text{O}i\text{-Pr})_4$ and $n\text{-BuLi}$,⁸ followed by exposure of the resulting organometallic intermediate to the Li-alkoxide of 14, and quenching with benzaldehyde resulted in the formation of the tricyclic carbocycle 15 in 59% yield (dr $\geq 20:1$, rs $\geq 20:1$). Similarly, coupling of the methoxy-substituted aromatic 16 with TMS-alkyne 12 delivered 17, again with exquisite levels of regio- and stereoselectivity (entry 3). As depicted in entries 4–6, this annulation reaction is also effective with a conjugated alkyne possessing a functionalized silane (18), as well as an alkynyl cyclopropane (21). Here, tricyclic products 19, 20, and 22 were generated in 64%, 48%, and 52% yield.

With these early examples demonstrating the ability to accomplish alkoxide-directed and Ti-mediated convergent annulation for the synthesis of angularly substituted decalins that contain a fused aromatic, we directed our attention toward realizing this annulation reaction with enynes that contain fully aliphatic tethers. As illustrated in entries 7–13, the annulation reaction is quite effective in this series, delivering stereodefined carbocyclic products in 53–71% yield. Notably, the metallacycle-mediated annulation reaction is also effective for the generation of linearly fused tricycles. As illustrated in entry 14

Table 1

Reaction scheme for Table 1: An enyne (with a methyl group, a hydroxyl group, and an alkyne) reacts with an alkyne in the presence of $\text{Ti}(\text{O}i\text{-Pr})_4$, $n\text{-BuLi}$, PhMe , -78 to 45 °C, and then PhCHO to form a tricyclic product.

entry	enyne	alkyne	yield (%)	product
1			—	
2			59	
3			59	
4			64	
5			48	
6			52	
7			53	
8			71	
9			61	
10			54	
11			71	
12			70	
13			56	
14			57	

Table 2

Reaction scheme for Table 2: An enyne (with a methyl group, a hydroxyl group, and an alkyne) reacts with an alkyne in the presence of $\text{Ti}(\text{O}i\text{-Pr})_4$, $n\text{-BuLi}$, PhMe , -78 to 50 °C, and then a protic quench at -78 or 0 °C to form a tricyclic product.

entry	enyne	alkyne	yield (%) (quench)	product
1			54 (CH ₃ OH)	
2			48 (CD ₃ OD)	
3			48 (CH ₃ OH)	
4			61 (NH ₄ Cl)	
5			54 (NH ₄ Cl)	
6			68 (NH ₄ Cl)	
7			54 (MeOH)	
8			64 (MeOH)	
9			43 (MeOH)	

^aQuenching with MeOH was conducted at -78 °C, while quenching with NH_4Cl (aq) was conducted at 0 °C.

of Table 1, union of enyne **36** with alkyne **12** proceeds to deliver the tricyclic product **37** in 57% isolated yield. In addition to nicely extending the scope of this annulation

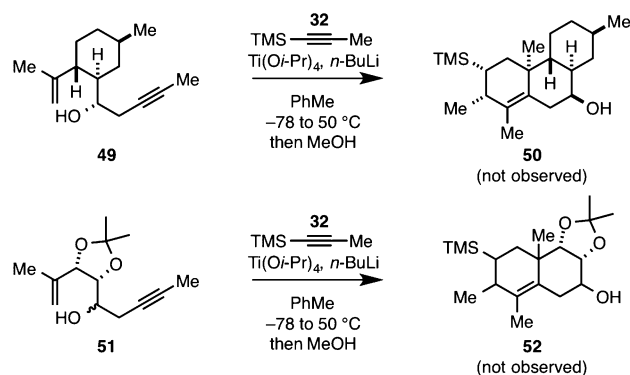


Figure 2. Success in this annulation is a function of substrate stereochemistry and substitution: Examples of substrates that failed in attempted annulation with TMS-propyne.

process to address the stereoselective synthesis of linearly fused tricycles, this is the first example of an alkoxide-directed annulation cascade that employs a tertiary alkoxide-containing enyne.

During the course of our studies we discovered that termination of the annulation reaction with a proton source results in the generation of a structurally unique product that harbors two additional stereocenters. For example, when reaction of enyne **14** with alkyne **12** is terminated with methanol at -78 °C (rather than quenching with benzaldehyde), the stereodefined reduced product of $[2 + 2 + 2]$, **38**, is generated in 54% yield (Table 2, entry 1). Here, stereoselectivity was quite high, positioning both the TMS- and PMP-group on the β -face of the carbocyclic product. When the reaction is instead quenched with CD_3OD , as in entry 2, the deuterated carbocycle **39** is generated. These observations are

consistent with the conclusion that the organometallic intermediate generated after $[4 + 2]$ cycloaddition has a lifetime that is sufficiently long to allow for manipulating the fate of this species down a reaction pathway that is distinct from our prior studies (cheletropic extrusion of titanium, or carefully orchestrated elimination reactions).

This reductive version of the alkoxide-directed Ti-mediated $[2 + 2 + 2]$ annulation is also effective with a conjugated alkyne (**18**), in this case delivering the functionalized carbocycle **40** in 48% yield (entry 3). In efforts focused on exploring the scope of this process, we found that in some cases quenching with aqueous ammonium chloride was more effective than with methanol. As illustrated in entries 4–6, reductive $[2 + 2 + 2]$ reactions between enyne **25** and alkynes **41**, **21**, and **12** are also effective, delivering the stereodefined products **42–44** in 61%, 54%, and 68% yield, respectively. Interestingly, as illustrated in entries 7–9, when the annulation reactions of enyne **25** with alkynes **45**, **12**, and **34** are quenched with methanol at -78 °C, structurally unique products of reductive annulation are generated. In the case of entries 7 and 8, reduction takes place in a net 1,4-manner to deliver the *cis*-fused carbocycles **46** and **47** in 54% and 64% yield, while, in entry 9, the major product **48** is the formal product of a regioisomeric 1,2 reduction that generates an isomeric *cis*-fused carbocycle (the structure of **48** was confirmed by X-ray diffraction data collected for a simple derivative; see Supporting Information for details).

While these results document the feasibility of accomplishing metallacycle-mediated $[2 + 2 + 2]$ for the convergent assembly of a variety of angularly substituted decalin-containing carbocycles, it is perhaps not surprising that some substrates were not compatible with the process. As described in Figure 2, enyne **49** could not be converted to carbocycle **50**, and the

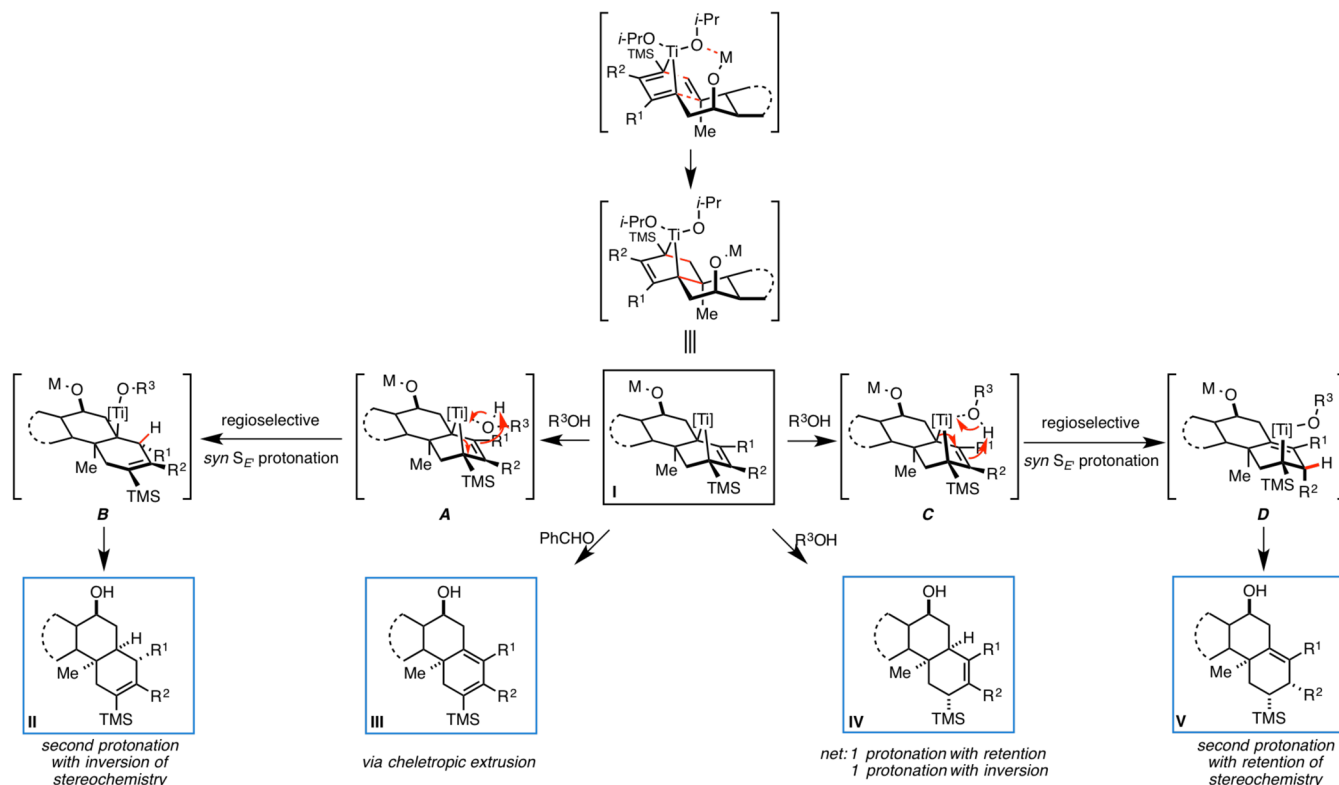


Figure 3. Summary of Ti-mediated annulation reactions en route to functionalized and angularly substituted decalins.

oxygenated enyne **51** (either isomer) could not be converted to **52**. In this latter case, each diastereomer of **51** was converted to the triene resulting from alkoxide-directed metallacycle-mediated alkyne–alkyne coupling⁷ without evidence being observed for progression of the reaction through the intramolecular [4 + 2] cycloaddition.

Our results have revealed that metallacycle-mediated intermolecular [2 + 2 + 2] annulation is a productive mode of reactivity for the convergent and stereoselective synthesis of angularly substituted decalin-containing carbocycles. Further, these studies have revealed an unexpected lifetime of the bridged polycyclic organometallic intermediate proposed to result from intramolecular cycloaddition. As depicted in Figure 3, exposure of this intermediate (generalized as structure **I**) to benzaldehyde results in cheletropic extrusion of the metal and production of a cyclohexadiene (**I** → **III**). Alternatively, quenching with methanol or ammonium chloride leads to one of three different reduced products. A simple model to visualize these stereoselective pathways is shown via initial regioselective *syn* S_E' protonation (**I** → **A** → **B**, or **I** → **C** → **D**), followed by a second protonation of the resulting tertiary organotitanium intermediate that proceeds with either inversion (**B** → **II**) or retention (**D** → **V**). Alternately, we have observed products that appear to result from direct protonation of the bridged bicyclic metallacycle but may derive from a more complex and less clear sequence of steps (**I** → **IV**). Surprisingly, the stereoselectivity associated with each pathway appears to be quite high, but distinguishing between and predicting which reaction path will predominate as a function of substrate structure or nature of the protic quench is less clear.

CONCLUSION

In summary, we have discovered a metal-centered reaction cascade for the convergent and stereoselective synthesis of angularly fused decalins. While defining the first convergent [2 + 2 + 2]-based strategy to accomplish such a feat, these investigations have also led to the elucidation of unique modes of reactivity associated with the presumed complex organometallic intermediates generated under the reaction conditions. We demonstrate cheletropic extrusion of the metal can be induced to proceed by addition of benzaldehyde, defining a highly stereoselective pathway to angularly substituted decalins that contain a highly substituted cyclohexadiene. Notably, we have also discovered that the complex organometallic intermediate in these annulations can be diverted away from this cheletropic reaction down one of several stereoselective pathways to generate reduced products of [2 + 2 + 2] annulation. While the nature of the proton source plays a role in path selectivity, so does the substrate structure; a relationship that has led to the discovery of three unique and powerful annulation reactions that generate three new C–C bonds and three new stereocenters, one of which is quaternary. We look forward to exploring the complexity of this reaction process and further investigating its utility in complex molecule synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and tabulated spectroscopic data for new compounds (PDF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02107.

AUTHOR INFORMATION

Corresponding Author

*glenn.c.micalizio@dartmouth.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the National Institutes of Health – NIGMS (GM80266) and postdoctoral fellowship support to HM from the Uehara Memorial Foundation.

REFERENCES

- (1) For reviews of metal-centered [2 + 2 + 2] annulation, see: (a) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1–8. (b) Aubert, C.; Buisine, O.; Petit, M.; Slowinski, F.; Malacria, M. *Pure Appl. Chem.* **1999**, *71*, 1463–1470. (c) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265–2291. (d) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209–2217. (e) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, *6*, 1317–1323. (f) Tanaka, K. *Chem.—Asian J.* **2009**, *4*, 508–518. (g) Leboeuf, D.; Gandon, V.; Malacria, M. Transition Metal-Mediated [2 + 2 + 2] Cycloadditions. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley–VCH: Weinheim, 2009; Vol. 1, p 367.
- (2) (a) González, M. A. *Nat. Prod. Rep.* **2015**, *32*, DOI: 10.1039/C4NP00110A. (b) Heasley, B. *Chem.—Eur. J.* **2012**, *18*, 3092–3120. (c) Chapelon, A.-S.; Moraléda, D.; Rodríguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron* **2007**, *63*, 11511–11616. (d) Godtfredsen, W. O.; von Daehne, W.; Vangedal, S.; Marquet, A.; Arigoni, D.; Melera, A. *Tetrahedron* **1965**, *21*, 3505–3530. (e) Zhao, M.; Gödecke, T.; Gunn, J.; Duan, J.-A.; Che, C.-T. *Molecules* **2013**, *18*, 4054–4080.
- (3) (a) Sternberg, E. D.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 4839–4841. (b) Sternberg, E. D.; Vollhardt, K. P. C. *J. Org. Chem.* **1982**, *47*, 3447–3450. (c) Clinet, J.-C.; Duñach, E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6710–6712. (d) Butenschön, H.; Winkler, M.; Vollhardt, K. P. C. *J. Chem. Soc., Chem. Commun.* **1986**, 388–390. (e) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2091–2093. (f) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006–4008. (g) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381–382.
- (4) (a) Greszler, S. N.; Reichard, H. A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2766–2774. For a recent review of alkoxide-directed metallacycle-mediated cross-coupling, see: (b) Micalizio, G. C.; Hale, S. B. *Acc. Chem. Res.* **2015**, *48*, 663–673.
- (5) Cheng, X.; Micalizio, G. C. *Org. Lett.* **2014**, *16*, 5144–5147. The cross-conjugated triene-containing hydrindanes produced by this coupling reaction served as substrates for intermolecular Diels–Alder cycloaddition reactions with a variety of highly activated dienophiles.
- (6) (a) Jeso, V.; Aquino, C.; Cheng, X.; Mizoguchi, H.; Nakashige, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 8209–8212. (b) Kim, W. S.; Aquino, C.; Mizoguchi, H.; Micalizio, G. C. *Tetrahedron Lett.* **2015**, *56*, DOI: 10.1016/j.tetlet.2015.01.029.
- (7) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764–2765.
- (8) (a) Obora, Y.; Moriya, H.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2003**, 2820–2821. (b) Rassadin, V. A.; Six, Y. *Tetrahedron* **2014**, *70*, 787–794. For the use of *n*-BuLi en route to Ti–imine complexes, see: (c) Tarselli, M. A.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4596–4599.