Carbocycles

Deutsche Ausgabe: DOI: 10.1002/ange.201606962
Internationale Ausgabe: DOI: 10.1002/anie.201606962

Synthesis of Angularly Substituted *trans*-Fused Decalins through a Metallacycle-Mediated Annulative Cross-Coupling Cascade

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Dedicated to Professor Stuart L. Schreiber on the occasion of his 60th birthday

Abstract: *A convergent coupling reaction is described that enables the stereoselective construction of angularly substituted trans-fused decalins from acyclic precursors. The process builds on our alkoxide-directed titanium-mediated alkyne–alkyne coupling and employs a 1,7-enyne coupling partner. Overall, the reaction is thought to proceed through initial formation of a tetrasubstituted metallacyclopentadiene, stereoselective intramolecular [4+2] cycloaddition, elimination, isomerization, and regio- and stereoselective protonation. Distinct from our early studies directed at the synthesis of trans-fused hydrindanes, the current annulative coupling reveals an important effect of TMSCl in controlling the final protonation—the event that establishes the stereochemistry of the ring fusion.*

Fused polycyclic carbocycles are ubiquitous in nature and medicine, and have served as both a testing ground for some of the most powerful complexity-generating methods in organic chemistry, and as a stimulus for the generation of novel synthesis strategies. Arguably one of the most powerful means of carbocycle construction is the Diels–Alder reaction, which is capable of forging C–C bonds in either an intra- or intermolecular fashion.[1] In the latter case, where one can capitalize on convergency to impact synthesis efficiency, such chemistry is broadly constrained to the formation of *cis* ring fusions (Figure 1 A). A notable exception to this is Danishefsky's program, which aims to define a *trans*-Diels–Alder paradigm.[2] While early studies were directed at preparing *trans*-fused systems lacking angular alkyl substitution, recent advances have resulted in a three-step sequence to prepare such systems with good levels of *trans*-selectivity (Figure 1 B).[3] Herein, we describe a new convergent one-step coupling process between TMS-substituted alkynes and 1,7-enynes that delivers angularly substituted *trans*-fused decalins through a complex metallacycle-mediated cross-coupling reaction cascade, and report an effect of TMSCl in controlling the selectivity of the process (Figure 1 C).

Recently, we reported a collection of metallacycle-mediated annulation methods for the synthesis of angularly substituted decalins that proceed through the union of

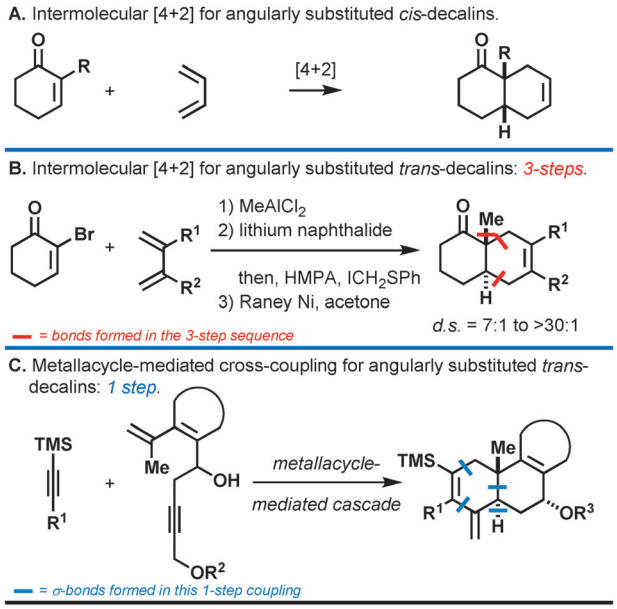

Figure 1. Use of convergent coupling chemistry to access decalins and the development of a metallacycle-mediated coupling process for the synthesis of angularly substituted *trans*-fused decalins.

TMS-alkynes with 1,7-enynes.[4] A subset of these were found to be useful for the establishment of *cis*-fused systems, yet none of the variants explored were capable of delivering *trans*-fused products. In an effort to overcome this limitation, we pursued development of the coupling process depicted in Figure 2. We drew inspiration from our earlier studies that resulted in a convergent strategy for the synthesis of *trans*-fused and angularly substituted hydrindanes[5] and reasoned that a *trans*-selective decalin-forming annulation could proceed through the following cascade: 1) alkyne–alkyne coupling to deliver a metallacyclopentadiene (**A**),[6] 2) stereoselective intramolecular [4+2] cycloaddition to generate **B**,[7] 3) elimination en route to a tertiary allylic metal species (**C**), 4) isomerization to a primary allylic organometallic compound (**D**), and 5) regio- and stereoselective protonation by a *syn*-S_E' mechanism.[5] This final protonation process has, on occasion, been difficult to control. In the hydrindane-forming annulation, protonation is selective for the generation of the *trans*-fused product when R^1 is branched, with varying results typically favoring the *cis* isomer when this substituent is not branched. Notably, the complexity of the protonation of the final allylic organometallic intermediate is further compounded by the ability to protonate at the sp^3 carbon of **D**,

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201606962.

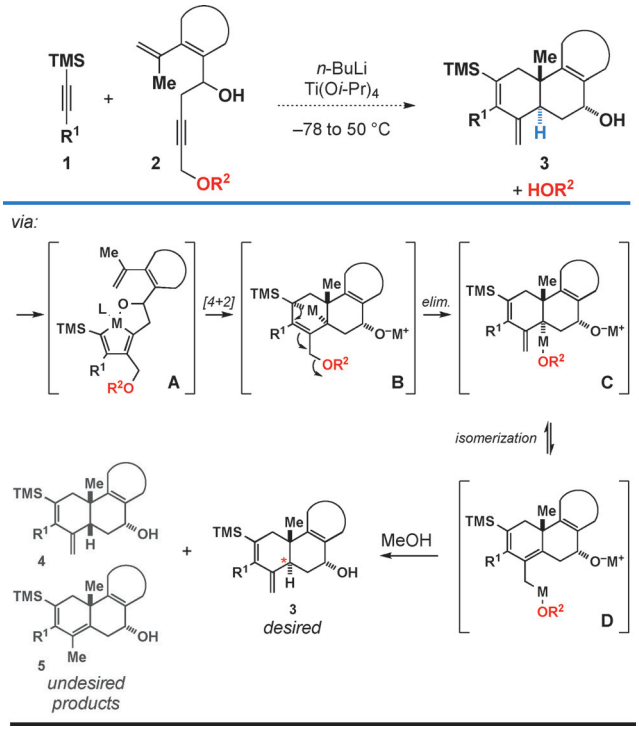


Figure 2. A planned pathway to angularly substituted *trans*-decalins through a metallacycle-mediated cross-coupling process.

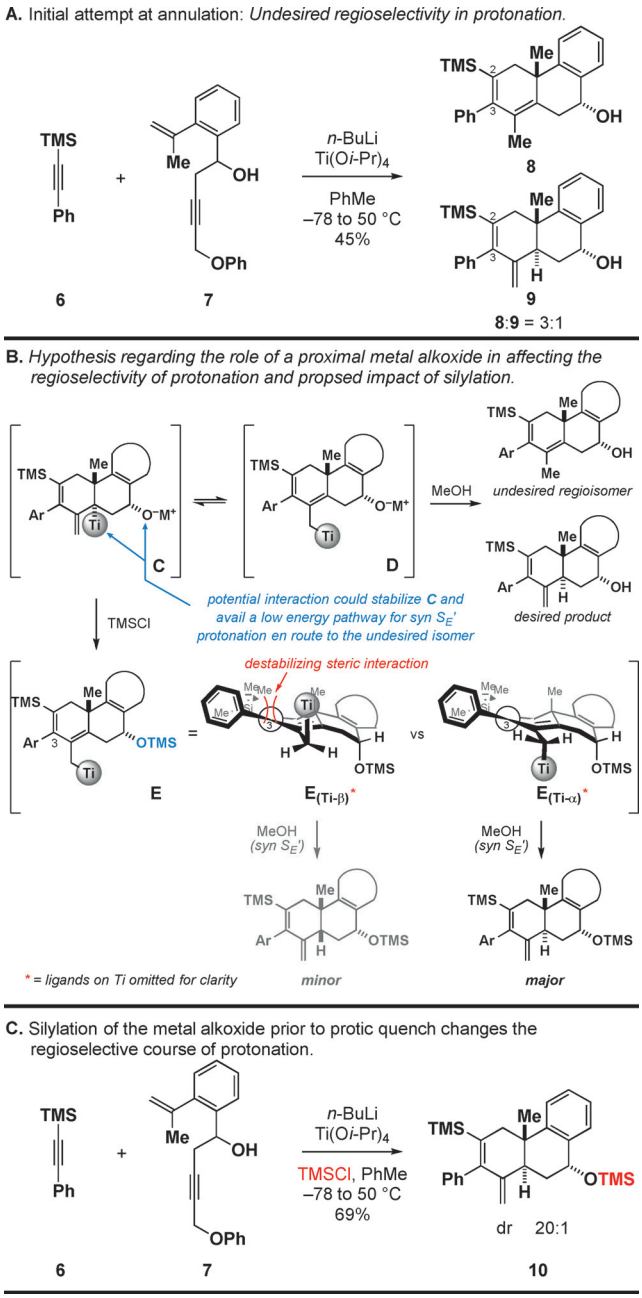


Figure 3. Initial observations: the role of TMSCl in the cross-coupling and cyclization cascade.

leading to an undesired product that possesses a cyclohexadiene motif (**5**).

Our inquiry began by investigating the coupling reaction of TMS-alkyne **6** with the 1,7-enyne **7** (Figure 3A).[8] As depicted, we found that this cascade process delivers a mixture of products favoring the formation of the undesired cyclohexadiene-containing species **8,** along with the desired *trans*-fused and angularly substituted decalin **9** (**8**/**9** = 3:1). Notably, both products were formed with high levels of selectivity: 1) regioselectivity in the initial alkyne–alkyne coupling, and 2) stereoselectivity for the angular stereocenter. These observations are consistent with our earlier investigations targeting the synthesis of angularly substituted hydrindanes and decalins.[4,5,7,9] Unfortunately, the regioselectivity seen in the protonation of the terminal organometallic species in the reaction cascade was both unexpected and undesired, showing a preference for the production of isomer **8**. We speculated that this result may derive from either a mechanistic ambiguity in the protonation of **D** (Figure 3B; competition between protonation with allylic transposition and direct protonation without allylic transposition) or interaction of the pendant metal alkoxide with the allylic organometallic part of **C** (highlighted in blue), thereby potentially stabilizing this isomeric allylic metal species and establishing a pathway to the undesired regioisomer (**8**) through protonation with allylic transposition.

In an attempt to disrupt this potential interaction between the metal alkoxide present in the central ring of the tricycle and the allylic organometallic part of intermediate **C** (Figure 3B), we pursued strategies to functionalize the carbocyclic alkoxide prior to protonation. For example, silylation would deliver a new allylic organometallic species (**E**) that may be less prone to undergo the undesired 1,3-isomerization. Protonation of this intermediate by a *syn* S_E' mechanism could proceed via either conformer $\mathbf{E}_{(Ti\text{-}\beta)}$ or $\mathbf{E}_{(Ti\text{-}\alpha)}$, the latter of which would deliver the desired *trans*-fused decalin product.

As illustrated in Figure 3C, the addition of TMSCl had a profound impact on selectivity.[10] With this simple experimental modification, coupling of TMS-alkyne **6** with enyne **7** delivered the angularly substituted *trans*-fused decalin **10** in 69% isolated yield, with no evidence being found for the production of a regio- or stereoisomeric product.

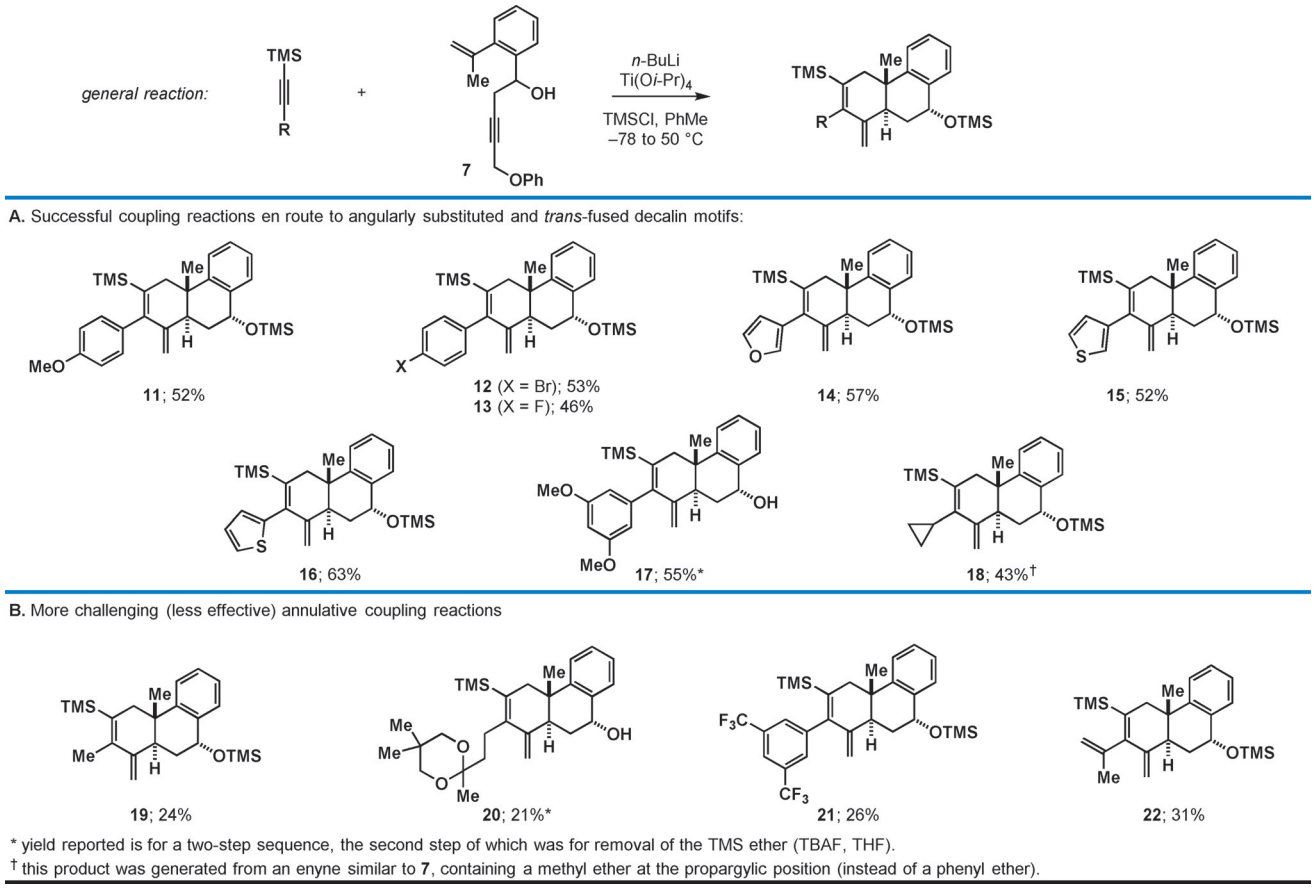


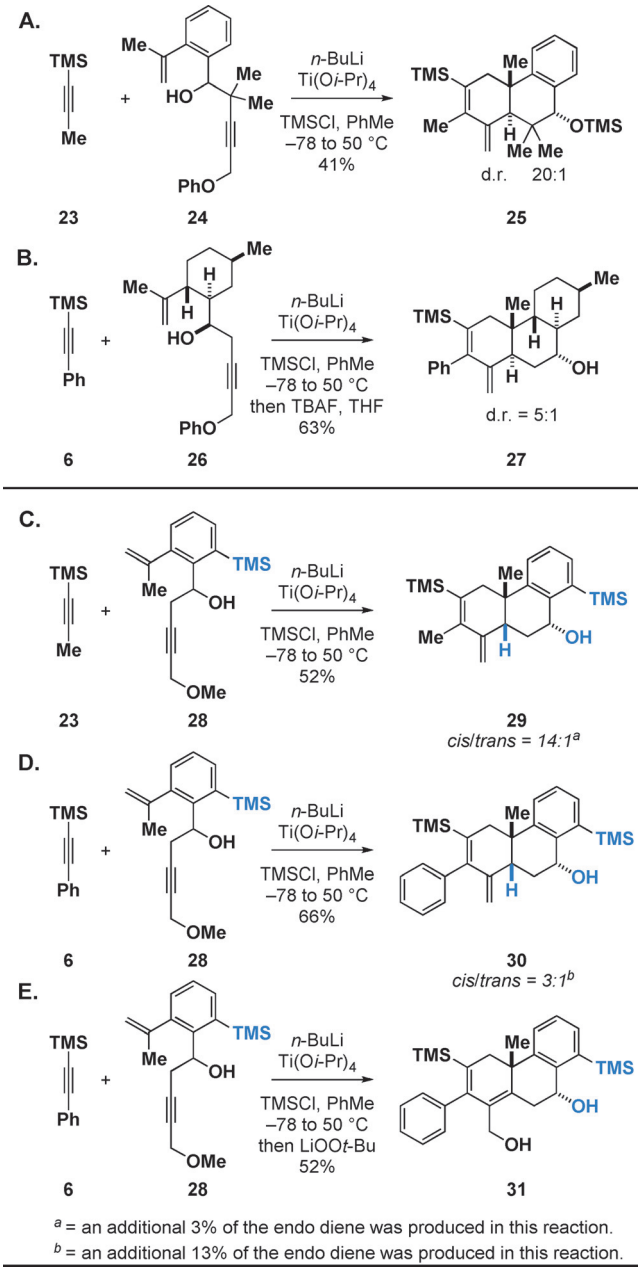
Figure 4. Scope with respect to the TMS-alkyne in annulation reactions with enyne **7**.

As depicted in Figure 4A, this coupling reaction was successful with a variety of TMS-alkynes, the most successful of which contain aromatic substituents (**11**–**18**). In all cases, no evidence was found for the production of regio- or stereoisomeric products. As is the case with most complex reaction processes in organic chemistry, this new annulative coupling reaction was found to have some limitations in scope. In general, attempts to couple enyne **7** with TMS-alkynes bearing typical aliphatic substituents proved substantially more difficult (Figure 4B). In most cases, a complex mixture of reaction products was observed, from which we were able to isolate up to 24% of the desired tricycle (see **19** and **20**). Similarly problematic were highly electron-deficient TMS-alkynes and one conjugated to a 1,1-disubstituted olefin (see products **21** and **22**). In these less effective annulation reactions, we recognized that the initial metallacycle-mediated alkyne–alkyne coupling is effective, but progression through the [4+2] cycloaddition competes with what appears to be a collection of as yet unidentified pathways for decomposition.

With this as a working hypothesis for the underperformance illustrated in Figure 4B, we moved forward with exploring enyne substrates that are more conformationally predisposed to undergo the requisite [4+2] reaction at a faster rate.As illustrated in Scheme 1A, an enyne possessing a propargylic quaternary center (**24**) was effective in annulative coupling with TMS-propyne **23** and delivered the angularly substituted *trans*-fused tricycle **25** in a modest 41% yield. This variation in efficiency (vs. that depicted in Figure 4B, i.e., **19**) is consistent with the Thorpe–Ingold effect,[11] and supports the hypothesis that the rate of the intramolcular [4+2] portion of this annulative coupling is an important consideration to maximize chances for success.

The enyne reaction partner can contain an aliphatic tether. As depicted in Scheme 1B, union of TMS-alkyne **6** with enyne **26** proceeded effectively to deliver the *trans*-fused and angularly substituted tricycle **27** in 63% yield (*trans*/*cis* = 5:1).

With intent to explore the effect of other substituents that would bias the conformation of the reactive metallacyclopentadiene-containing intermediate to support the critical intramolecular [4+2] process, we explored a variant of enyne **7** that contains an *o*-TMS substituent. As illustrated in Scheme 1C, coupling of TMS-propyne (**23**) with enyne **28** was effective. In this case, we were able to isolate a mixture of tricyclic products in 52% yield. Surprisingly, the major product isolated here (**29**) was found to contain a free alcohol at the benzylic position (rather than the previously observed TMS-ether) and, perhaps more interestingly, a *cis* ring fusion (*cis*/*trans* = 14:1). A similar stereodivergence was found in the related coupling of **28** with TMS-phenylacetylene **6** (Scheme 1D), albeit proceeding with lower levels of *cis*-selectivity (3:1). The mechanistic source of stereodivergence observed with these annulation reactions remains unclear, but



Scheme 1. Exploration of scope with respect to the enyne structure.

we note that oxidative termination of the annulation process, as in Scheme 1 E, delivers a primary allylic alcohol that is expected to be a useful intermediate in numerous well-established transformations (e.g., directed epoxidation, hydrogenation, and cyclopropanation,[12] as well as [2,3]- and [3,3]-sigmatropic rearrangement chemistry,[13] among others).

In conclusion, we have discovered a complex annulative cross-coupling that delivers angularly substituted and *trans*-fused decalins through a complex orchestrated sequence of transformations that occurs in a single pot. These investigations have revealed an important effect of TMSCl in controlling the final step of the process that, in most cases, establishes the *trans* fusion of the system. To our knowledge, this reaction process represents the first of its kind, providing access to angularly substituted *trans*-fused decalins through an intermolecular reaction that establishes both ring systems in a single reaction of significant complexity. We look forward to further developing this complex annulation reaction, exploring the role that substituents play in the course of these transformation, and applying them in target- and function-oriented synthesis.

Acknowledgements

We acknowledge financial support from the National Institutes of Health—NIH GM080266. H.M. gratefully acknowledges postdoctoral fellowship support from the Japan Society for the Promotion of Science (JSPS).

Keywords: carbocycles · cascade reactions · cross-coupling · cycloadditions · Diels–Alder reactions

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 13099–13103
Angew. Chem. **2016**, *128*, 13293–13297

[1] A recent review of the Diels–Alder reaction in total synthesis: K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698; *Angew. Chem.* **2002**, *114*, 1742–1773.

[2] a) W. H. Kim, J. H. Lee, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12576–12578; b) R. S. Paton, J. L. Mackey, W. H. Kim, J. H. Lee, S. J. Danishefsky, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 9335–9340.

[3] J. H. Lee, Y. Zhang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 14330–14333.

[4] H. Mizoguchi, G. C. Micalizio, *J. Am. Chem. Soc.* **2015**, *137*, 6624–6628.

[5] V. Jeso, C. Aquino, X. Cheng, H. Mizoguchi, M. Nakashige, G. C. Micalizio, *J. Am. Chem. Soc.* **2014**, *136*, 8209–8212.

[6] J. Ryan, G. C. Micalizio, *J. Am. Chem. Soc.* **2006**, *128*, 2764–2765.

[7] S. N. Greszler, H. A. Reichard, G. C. Micalizio, *J. Am. Chem. Soc.* **2012**, *134*, 2766–2774.

[8] Alkoxide-directed [2+2+2] annulation reactions between alkynes and enynes have been demonstrated with symmetric (Ref. [7]) and unsymmetric alkynes. We focused the current studies on the use of unsymmetrical alkynes due to the expected synthetic relevance of the products formed. TMS-alkynes are particularly well suited for regioselective coupling reactions in this class (Ref. [9]), although some differentially substituted internal alkynes can be used in regioselective alkyne–alkyne coupling reactions (see Ref. [6]). The first step of this annulation process for the synthesis of *trans*-fused and angularly substituted decalins.

[9] This regioselectivity is consistent with our earlier investigations of alkyne–alkyne coupling, as well as other examples of [2+2+2] annulation. See Refs. [4,5,10] and: a) F. Kolundzic, G. C. Micalizio, *J. Am. Chem. Soc.* **2007**, *129*, 15112–15113; b) T. K. Macklin, G. C. Micalizio, *J. Am. Chem. Soc.* **2009**, *131*, 1392–1393; c) T. K. Macklin, G. C. Micalizio, *Nat. Chem.* **2010**, *2*, 638–643; d) D. P. Canterbury, G. C. Micalizio, *J. Am. Chem. Soc.* **2010**, *132*, 7602–7604; e) P. S. Diez, G. C. Micalizio, *J. Am. Chem. Soc.* **2010**, *132*, 9576–9578; f) V. Jeso, G. C. Micalizio, *J. Am. Chem. Soc.* **2010**, *132*, 11422–11424; g) X. Cheng, G. C. Micalizio, *Org. Lett.* **2014**, *16*, 5144–5147; h) W. S. Kim, C. Aquino, H. Mizoguchi, G. C. Micalizio, *Tetrahedron Lett.* **2015**,

56, 3557 – 3559; i) X. Cheng, G. C. Micalizio, *J. Am. Chem. Soc.* **2016**, *138*, 1150 – 1153; j) C. Aquino, S. N. Greszler, G. C. Micalizio, *Org. Lett.* **2016**, *18*, 2624 – 2627; k) K. Harada, H. Urabe, F. Sato, *Tetrahedron Lett.* **1995**, *36*, 3203 – 3206; For recent reviews, see: l) H. A. Reichard, M. McLaughlin, M. Z. Chen, G. C. Micalizio, *Eur. J. Org. Chem.* **2010**, 391 – 409; m) A. Wolan, Y. Six, *Tetrahedron* **2010**, *66*, 3097 – 3133.

[10] A recent report describing the effect of TMSCl on a metallacycle-mediated cross-coupling between alkynes: J. S. Cassidy, H. Mizoguchi, G. C. Micalizio, *Tetrahedron Lett.* **2016**, *57*, 3848 – 3850.

[11] A recent review: M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735 – 1766.

[12] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307 – 1370.

[13] a) T. Nakai, K. Mikami, *Org. React.* **1994**, *46*, 105 – 209; b) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423 – 1452; c) R. A. Fernandes, A. K. Chowdhury, P. Kattanguru, *Eur. J. Org. Chem.* **2014**, 2833 – 2871.

Received: July 18, 2016
Published online: September 16, 2016

