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

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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 by 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 has revealed an important effect of TMSCl in controlling the final protonation – the event that establishes the ring fusion stereochemistry.

Graphical abstract

Three C-C sigma bonds and two stereocenters, one of which is quaternary, are formed in this annulative cross-coupling reaction that furnishes polycyclic carbocycles containing an angularly substituted and *trans*-fused decalin.

Keywords

metallacycle-mediated cross-coupling; Diels-Alder cycloaddition; carbocycle; tandem reaction

Fused polycyclic carbocycles are ubiquitous in nature and medicine, having served as both a testing ground for among the most powerful complexity-generating methods in organic chemistry, and as stimuli for the generation of novel synthesis strategies. Arguably one of the most powerful means for carbocycle construction is the Diels-Alder reaction, 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 1A). A notable exception to this is Professor Danishefsky's program that 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 1B).^[3] Here, 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 1C).

Recently, we reported a collection of metallacycle-mediated annulation methods for the synthesis of angularly substituted decalins that proceed through the union of 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 by the following tandem reaction: (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 (**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 “R¹” 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 sp³ carbon of **D**, 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 (eq. 1)].^[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 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 in **C** (highlighted in blue), potentially stabilizing this isomeric allylic metal species and establishing a pathway to the undesired regioisomer (i.e. **8**) via 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 in 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 1,3-isomerization. Protonation of this intermediate by a *syn* S_E' mechanism could proceed by either conformer **E**_(Ti- β) or **E**_(Ti- α), the latter of which would deliver the desired *trans*-fused decalin product.

As illustrated in Figure 3C (eq 2), 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.

As depicted in Figure 4A, this coupling reaction was successful with a variety of TMS-alkynes, the most successful of which contain aromatic substituents (i.e. **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 is competitive 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 eq. 3 (Scheme 1), 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% isolated yield. This variation in efficiency is consistent with the Thorpe-Ingold effect,^[11] and supports the hypothesis that rate of the intramolecular [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 eq 4 of Scheme 1, 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 eq. 5 of Scheme 1, 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** (eq. 6), albeit proceeding with lower levels of *cis*-selectivity (3:1). The mechanistic source of stereodivergence observed with these annulation reactions remains unclear, but we note that oxidative termination of the annulation process, as in eq. 7, delivers a primary allylic alcohol that is expected to be a useful intermediate in numerous well-established transformations (i.e. 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 effecting the course of these transformation, and applying them in target- and function-oriented synthesis.

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A. Intermolecular [4+2] for angularly substituted *cis*-decalins. **B.** Intermolecular [4+2] for angularly substituted *trans*-decalins: **3-steps**. **C.** Metallacycle-mediated cross-coupling for angularly substituted *trans*-decalins: **1 step**. **Figure 1.**

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

Figure 2.

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

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

A. Successful coupling reactions en route to angularly substituted and *trans*-fused decalin motifs:

B. More challenging (less effective) annulative coupling reactions

* yield reported is for a two-step sequence, the second step of which was for removal of the TMS ether (TBAF, THF).

† this product was generated from an enyne similar to 7, containing a methyl ether at the propargylic position (instead of a phenyl ether).

Figure 4.
Scope of the TMS-alkyne in annulation reactions with enyne 7.

Scheme 1.
 Exploration of scope regarding enyne structure.