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LiOO*t*-Bu as a terminal oxidant in a titanium alkoxide-mediated [2+2+2] reaction cascade☆

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Abstract

LiOO*t*-Bu is an effective oxidant for converting the penultimate organometallic intermediate generated in a titanium alkoxide-mediated [2+2+2] reaction cascade to an allylic alcohol. Oxidation of the presumed allylic titanium species is highly regioselective, providing direct access to substituted hydroindanes containing a primary allylic alcohol. In addition to demonstrating the feasibility of this oxidation process, we document the ability to convert the primary allylic alcohol products to angularly substituted *cis*-fused hydroindanes.

Keywords

Metallacycle-mediated cross-coupling; Cascade reaction; Oxidation; Hydroindanes; [2+2+2]

Metallacycle-mediated cross-coupling, processes that allow for the union of unsaturated substrates through the formation of metallacyclopentane intermediates by formal [2+2+1], is growing as a particularly powerful mode of chemical reactivity for stereoselective synthesis.[1] While early discoveries were reported over sixty years ago, challenges associated with the control of reactivity and selectivity have lingered, negatively impacting the potential utility of this type of reactivity in complex molecule synthesis. Over the last decade a great variety of metallaycle-mediated coupling reactions for the union of alkynes with aldehdyes/imines have emerged,[2] with recent advances demonstrating that coupling between alkenes, alkynes and allenes can now be accomplished with regio- and stereocontrol.[1,3] In studies associated with our desire to develop this latter area of coupling technology, we recently discovered a metallacycle-mediated annulation reaction between TMS-alkynes (**1**) and 1,6-enynes (**2**) that produces angularly substituted hydroindanes (**3**) with outstanding levels of diastereoselectivity (> 20:1; Figure 1A).[4] Experiments aimed at understanding the mechanism for this process led to the proposal that this [2+2+2] annulation process proceeded by initial alkoxide-directed alkyne–alkyne coupling (→ **I**),[5] followed by intramolecular [4+2] cycloaddition (→ **II**), and finally cheletropic extrusion of the metal

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Supplementary Material

Experimental procedures, NMR spectra, and tabulated spectroscopic data for new compounds (PDF) are included as supporting information for this manuscript.

center. When the enyne coupling partner possesses a distal propargylic ether (**4**), we found that the annulation sequence is interrupted by an elimination that traps the otherwise fleeting organometallic intermediate **III** (Figure 1B). The result of this elimination is the production of an allylic titanium species **IV** that is converted to *trans*-fused hydroindane products by protonation (*trans*-selectivity is highest when R^1 is branched).[6] While successful, this process often delivers a mixture of hydroindane products that are contaminated with an undesired alkene isomer that likely results from protonation at the primary carbon of the allylic metal system (→ **6**; – this isomer is often difficult to remove from the *trans*-fused hydroindane product). Here, we demonstrate that the penultimate organometallic intermediate generated in this alkoxide-directed metallacycle-mediated [2+2+2] annulation/elimination process (i.e. **IV**) can be regioselectively oxidized with LiOO*t*-Bu to deliver a hydroindane product containing a primary allylic alcohol (**7**) (Figure 1C). Outside of describing the first oxidation of such an intermediate in a metallacycle-mediated cascade reaction, subsequent reduction by way of an intermediate allylic diazene stereoselectively delivers *cis*-fused hydroindane products (**9**) (Figure 1D).

Our studies began by investigating the coupling reaction of TMS-alkyne **10** with the phenoxy-substituted enyne **11**. Here, we employed the now standard reaction conditions for [2+2+2] annulation, where exposure of **10** to the combination of $Ti(O\textit{i}\text{-}Pr)_4$ and *n*-BuLi (2 equiv) [7] is followed by introduction of the Li-alkoxide of enyne **11** (Scheme 1, eq 1). After warming from −78 °C to rt, a solution of LiOO*t*-Bu[8] is added. To our delight, the substituted hydroindane **12** that contains a primary allylic alcohol was produced as a single regio- and stereoisomer in 50% yield. While we anticipated the high regioselectivity associated with differential functionalization of the TMS-alkyne, and high diastereoselection of the process, we were delighted to observe the similarly high selectivity in regioselective oxidation. In this case, we did not identify any products derived from oxidation at the ring fusion (i.e. **8**, Figure 1C). While the yield of the process was 50%, the efficiency of the oxidation is high – termination of the annulation sequence with methanol delivers hydroindane products in 63% yield [52% of a 5:1 mixture of isomers (*trans:cis*) and 11% of the endocyclic diene; i.e. **6**, Figure 1B].[6]

As illustrated in equations 2–5 of Scheme 1, the oxidative termination of this [2+2+2] annulation reaction is effective for a variety of substrates, defining a concise route to a range of angularly substituted hydroindane products. As depicted in eqs 6 and 7 of Scheme 1, this procedure for oxidation has not been successful in the context of related titanium alkoxide-mediated coupling reactions. For example, with the identical conditions being employed for generation of the initial Ti-alkyne complex, coupling of TMS-alkyne **10** with allylic alcohol **22**, followed by addition of LiOO*t*-Bu did not deliver the expected acylsilane **23** (eq 6) -- only the product of simple reductive cross-coupling was observed.[9] Oxidative termination of an alkyne–alkyne coupling process was similarly ineffective (eq 7).

With this interrupted [2+2+2] annulation/oxidation in hand, we quickly turned our attention to exploring the reactivity of the primary allylic alcohol-containing products in reductive transposition chemistry. As illustrated in Scheme 2, we treated the annualtion product **12** with *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH), PPh_3, and DIAD in

THF.[10] To our delight, this process delivered the *cis*-fused hydroindane **25** in 63% (ds = 6:1). This is in contrast to our earlier studies that demonstrated *trans*-selectivity (ds = 1:5) if this annulation reaction is quenched with methanol.[6] Selectivity for formation of the *cis*-fused hydroindane product was also observed in reductive transposition of the structurally related allylic alcohols **14** and **16**. Here, the *cis*-fused hydroindane products **26** and **27** were produced in 57 and 60% yields (ds = 5:1 and 6:1, respectively).

In conclusion, we have demonstrated that LiOO*t*-Bu is an effective terminal oxidant in an "interrupted" titanium alkoxide-mediated [2+2+2] annulation. Unlike termination of the annulation process by protonation, this oxidation proceeds with exquisite levels of regioselectivity and affords primary allylic alcohol-containing hydroindane products. These stereodefined allylic alcohols are good substrates for IPNBSH-mediated reductive transposition, paving a stereoselective convergent pathway to densely functionalized and angularly substituted *cis*-fused hydroindanes. For substrates that are known to deliver *trans*-fused hydroindanes from Ti-mediated [2+2+2] and quenching with MeOH (i.e. **11** → **28**, and **13** → **29**; Figure 2),[6] the present LiOO*t*-Bu oxidative termination of the [2+2+2] and subsequent IPNBSH-mediated reduction defines a complementary approach for production of the isomeric *cis*-fused products (i.e. **11** → **25**, and **13** → **26**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

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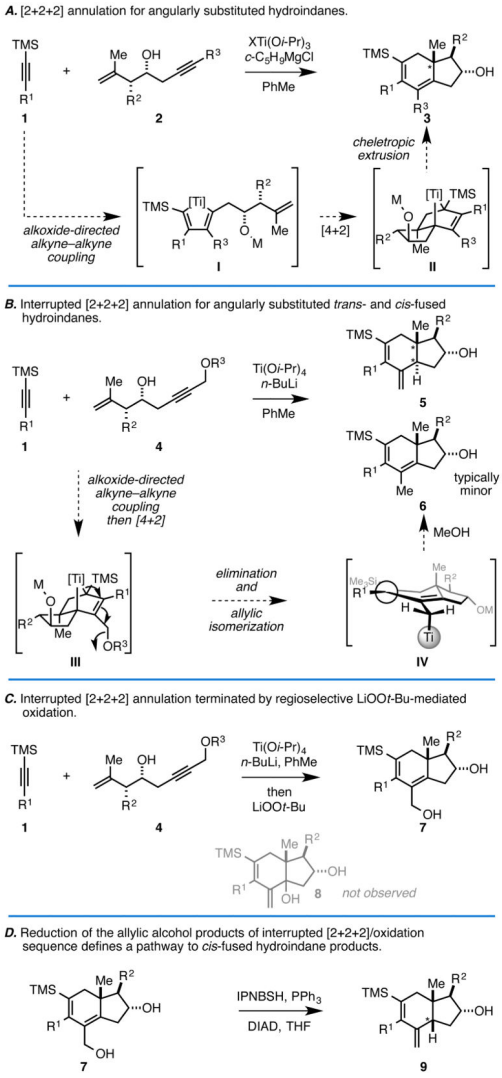
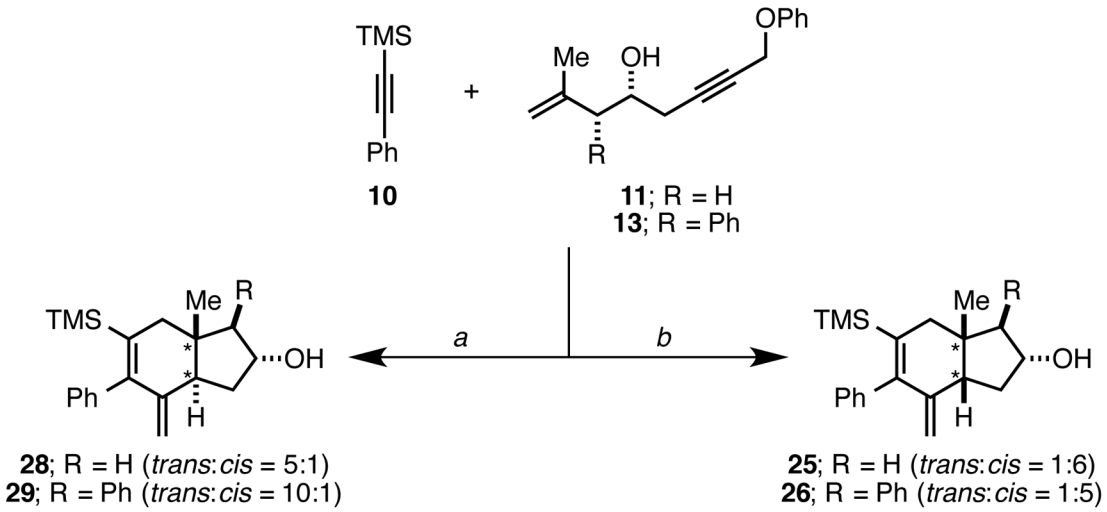


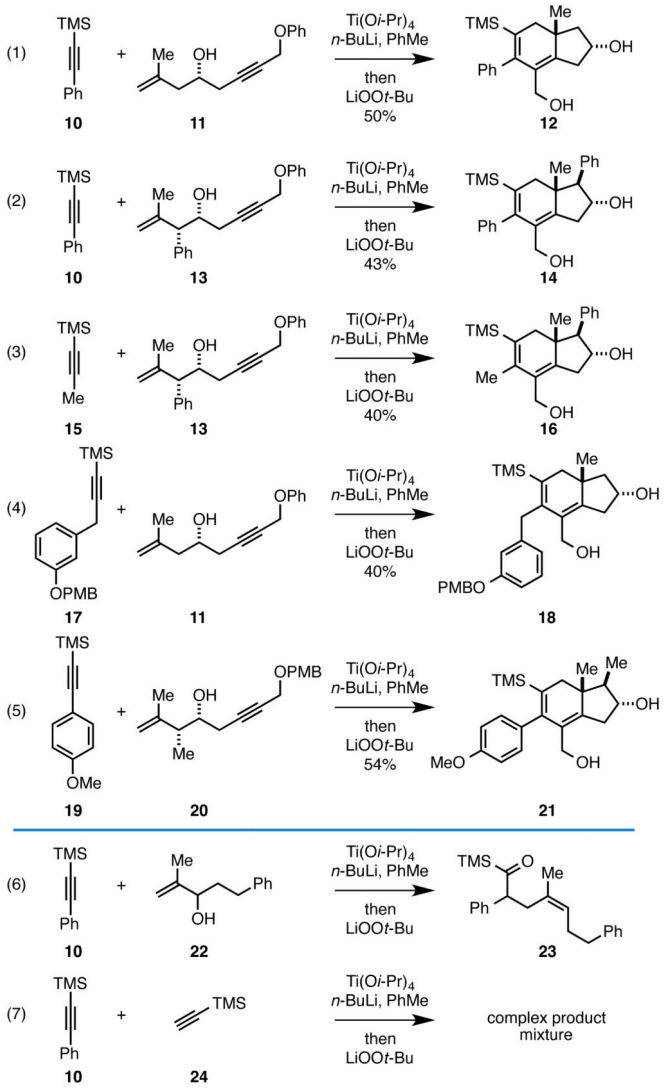
Figure 1.

Metallacycle-mediated convergent assembly of densely functionalized hydroindanes: Early discoveries (**A** and **B**), the development of an interrupted annulation-oxidation pathway (**C**), and the realization of a sequence to generate *cis*-fused and angularly substituted hydroindanes (**D**).



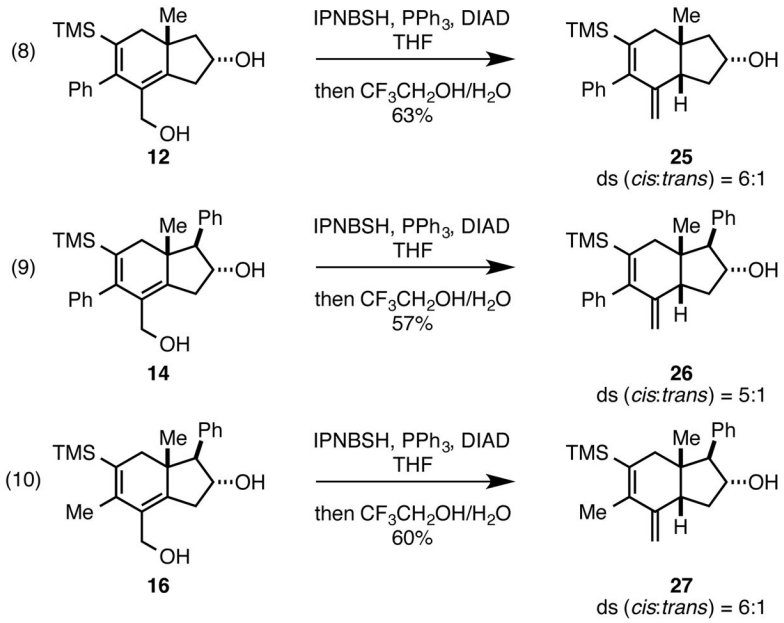
Reaction conditions: *a* = Ti(O*i*-Pr)$_4$, *n*-BuLi, PhMe, then MeOH. *b* = 1) Ti(O*i*-Pr)$_4$, *n*-BuLi, PhMe, then LiOO*t*-Bu; 2) IPNBSH, PPh_3, DIAD, THF, then CF_3CH_2OH/H_2O.

Figure 2.
Stereodivergent strategies for the synthesis of angularly substituted hydroindanes.



Scheme 1.

Tandem [2+2+2], elimination, and oxidation en route to angularly substituted hydroindanes: The oxidation procedure is not successful with alkyne–allylic alcohol or alkyne–alkyne coupling reactions.



Scheme 2.

Stereoselective reductive transposition of the allylic alcohol-containing products delivers *cis*-fused hydroindanes.