

ALKOXIDE-DIRECTED METALLACYCLE-MEDIATED INTERMOLECULAR [2+2+2] ANNULATION

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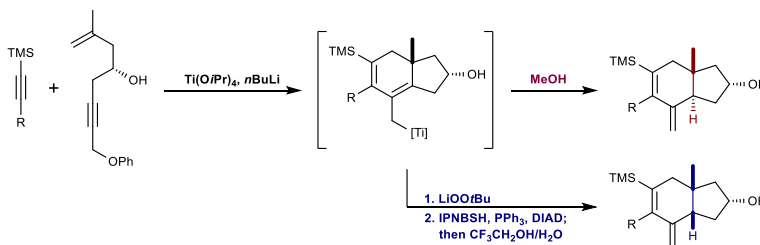
INTRODUCTION

The formation of C-C bonds played an essential role in the synthesis of organic compounds and has led to the development of many powerful C-C bond forming processes. However, there exists significant limitations in the use of this field of methodology. To avoid challenges in regioselectivity, intermolecular [2+2+2] requires the use of at least one symmetric coupling partner.¹ Furthermore, species undergoing reaction have been constrained to minimally substituted, unhindered species. Considering major issues in the selectivity and in controlling the reactivity of intermolecular [2+2+2] reactions, the Micalizio group sought to develop a new method that would favor cross-coupling over homo-coupling, decrease sensitivity to non-bonded steric interactions, and offer the ability to be both regioselective and stereoselective using unsymmetrical coupling partners.² To do this, $\text{Ti}(\text{OiPr})_4$ was chosen due to its rapid and reversible ligand exchange with hydroxy group, affording both a stereoselective and regioselective control via an alkoxide directing group.

TRANS- AND CIS-FUSED ANGULARLY SUBSTITUTED HYDRINDANES

Hydrindanes are a structural motif encountered in natural products and pharmaceuticals. Synthetic methods for the construction of hydrindanes have previously been limited to cycloaddition and Robinson annulation, each of which

Scheme 1. Synthesis of *Trans*- and *Cis*-Fused Hydrindanes



maintain difficulty in accessing enantiodefined, highly substituted, and/or oxygenated systems.³ Thus, alterations of stereochemistry, synthetic manipulations to increase complexity, and oxidative adjustments are often required. However, with the development of an alkoxide-directed metallacycle mediated [2+2+2] intermolecular cross-coupling reaction, a single regio- and stereoisomeric product may be produced in high complexity. Notable, use of the directing group overrides steric effects, preferring C-C bond formation distal to the free hydroxyl despite the nature of the proximal substituent. As the reaction proceeds, the oxametallacyclopentane formed from the alkoxide-directed alkyne-alkyne coupling undergoes alkoxide-promoted cleavage, followed by a stereoselective, metal-centered [4+2] and

chelotropic extrusion. In what is formally an interrupted [2+2+2] annulation, both *trans*- and *cis*-fused hydrindanes can be synthesized depending on the terminating conditions applied (Scheme 1).⁴ Through this reaction, two stereocenters and three C-C bonds are formed.

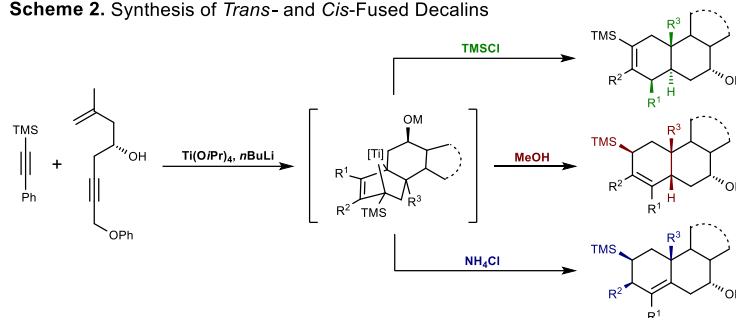
TRANS- AND CIS-FUSED ANGULARLY SUBSTITUTED DECALINS

Since the [4+2] bridged bicyclic can be trapped via various elimination processes, modification to the intermolecular [2+2+2] annulation can give both *trans*- and *cis*-fused decalins.² Termination of the cycloaddition product by site and stereoselective protonation can access highly functionalized, stereochemically rich decalins. The products

of the defined protic quenching with TMSCl, MeOH, or NH₄Cl (Scheme 2) afford access to three new stereocenters, one of which is quaternary, along with three C-C bonds.⁵ Using MeOH or NH₄Cl, an initial

regioselective *syn* SE' protonation occurs, which may be followed by a second protonation event if desired. Most notable of these reactions is the TMSCl quenched product. Without TMSCl, the intermediate with titanium at the fused ring junction is stabilized by the metal alkoxide, yielding undesired regioselectivity. However, use of TMSCl, alleviates this issue, forcing the titanium back to the allylic intermediate for selective formation of the *trans*-fused decalin.

Scheme 2. Synthesis of *Trans*- and *Cis*-Fused Decalins



SUMMARY AND OUTLOOK

With a rapid way to develop *trans*- and *cis*-fused hydrindanes and decalins, this intermolecular annulation has the potential to synthesize natural products or pharmaceuticals in less steps. Additionally, since how the reaction is quenched can lead to different skeletal structures, this reaction also offers the potential for diversification, expanding its utility to even more structural motifs.

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