

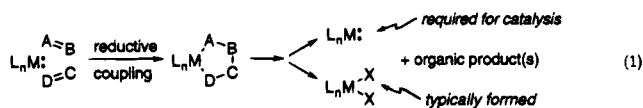
Titanium-Catalyzed Reductive Cyclization of δ,ϵ -Unsaturated Ketones and Aldehydes

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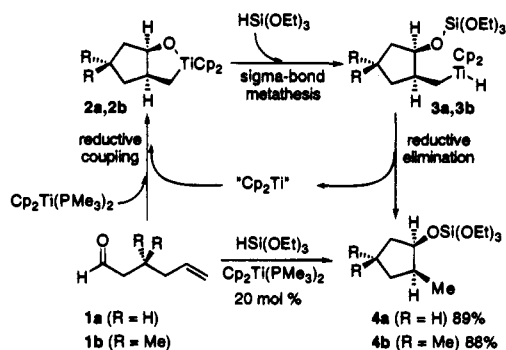
Transition metal mediated reductive coupling of a pair of unsaturated organic molecules results in the formation of a metallacyclopentane with concomitant formation of a carbon–carbon bond (eq 1). This reaction has been intensively studied for *in situ* generated early metal metallocenes (e.g., Cp_2Ti , Cp_2Zr , and Cp_2Hf)¹ and related reduced metal species. Although various protocols have been developed for the formation of useful organic products via selective metallacyclopentane cleavage, typical proteolytic or oxidative cleavage reactions produce a byproduct transition metal species (L_nMX_2 in eq 1) in the wrong oxidation state to effect further reductive coupling reactions. Thus, while the synthetic utility of zirconium- and titanium-mediated reductive coupling reactions is well established, the majority of processes developed to date use stoichiometric quantities of transition metal reagent. In cases where the transition metal reagent is not easily prepared (e.g., complexes employing expensive chiral, nonracemic ligands), catalytic processes become highly desirable. Described below is the successful development of such a catalytic process in our laboratories.



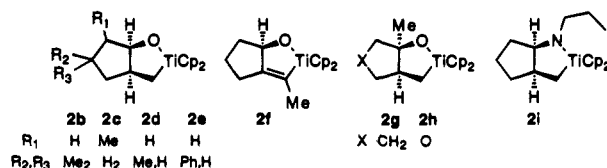
Whitby and Hewlett² reported that δ,ϵ -unsaturated carbonyl compounds react with $Cp_2Ti(PMe_3)_2$ to afford bicyclic titanium oxametallacycles (e.g., **1a** \rightarrow **2a** in Scheme 1). We felt that silane-mediated reductive cleavage of these oxametallacycles might be possible via the reaction sequence **2** \rightarrow **3** \rightarrow **4** depicted in Scheme 1. We envisioned that conversion of **2** to **4** would take place via σ -bond metathesis followed by reductive elimination from reactive intermediate **3**. One might worry that the strength of the titanium–oxygen bond in **2** would render any protocol which required the rupture of this bond to be a dim prospect. However, precedent for the σ -bond metathesis reaction can be found in the titanium-catalyzed, silane-mediated reductions of organic carbonyl substrates recently reported by Buchwald.³

Titanium metallacycle **2a** was prepared from 5-hexenal (**1a**) and $Cp_2Ti(PMe_3)_2$ as described by Whitby and Hewlett. Complex **2a** was treated with readily available silanes Et_3SiH , Ph_2SiH_2 , and $(EtO)_3SiH$. Although no reaction occurred between Et_3SiH and **2a**, Ph_2SiH_2 and $(EtO)_3SiH$ cleanly converted **2a** to silyl-protected cyclopentanol **4a**. The same cleavage reaction was attempted for each of the metallacycles listed in Scheme 2 using $(EtO)_3SiH$ as the silane reagent.⁴ For oxametallacycles (**2a–g**) the silane cleavage proved to be a clean, high-yielding reaction (75–91%). In many cases it proved to be more efficient than proteolytic cleavage. Silane

Scheme 1



Scheme 2



cleavage of oxametallacycle **2h** was less clean but produced the desired organic product in 50% yield. For azametallacycle **2i**, no cleavage took place.

Since the reductive elimination step **3** \rightarrow **4** should initially produce a reactive titanocene species, a catalytic cycle can be envisioned for the reductive cyclization of δ,ϵ -unsaturated carbonyl compounds (Scheme 1, overall transformation **1** \rightarrow **4**). Indeed, when 5-hexenal (**1a**) or 3,3-dimethyl-5-hexenal (**1b**) was treated with $(EtO)_3SiH$ (1 equiv) in the presence of a catalytic quantity (20 mol %) of $Cp_2Ti(PMe_3)_2$, reductive cyclization products were obtained in good yield.⁵

We next examined the stereoselectivity of the reductive cyclization reaction for some chiral substrates. Methacrolein, crotonaldehyde, and cinnamaldehyde were converted to 2- and 3-substituted 5-hexenal substrates via allyl anion addition followed by oxy-Cope rearrangement.⁶ Cyclization of 3-substituted substrates proceeded unselectively (eq 2), while cyclization of 2-methyl-5-hexenal gave a 4:1 mixture of isomers (Scheme 3). The major diastereomer produced in the cyclization of 2-methyl-5-hexenal possessed diastereotopic methyl groups indicating *trans,cis*-**4c**, while the minor diastereomer had equivalent methyl groups indicating structure *cis,cis*-**4c**. The stereochemistry of the major *trans,cis* isomer arises from the tendency of the α -methyl substituent to get placed on the convex side of the bicyclic metallacycle intermediate *exo*-**2c**. The 1,2-asymmetric induction observed in the reductive coupling step is of the same sense as that observed in analogous intramolecular cycloaddition⁷ and enyne bicyclization⁸ reactions. This selectivity is consistent with a reactive conformer **1c-TiCp₂** which places the methyl group in a pseudoequatorial position.

(4) Whitby and Hewlett reported that cocyclization reactions of ketones to both alkenes and alkynes failed in attempts to form six-membered rings.² We found that similar reactions of the aldehyde substrate 6-hexenal also failed to produce the desired six-membered-ring products.

(5) A representative experimental procedure: To a solution of $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol) in pentane (10 mL) was added 5-hexenal (98 mg, 1.0 mmol). The reaction mixture was stirred for 0.5 h and then treated with triethoxysilane (185 μ L, 1.0 mmol). The resulting mixture was stirred for 3 h, exposed to air, then passed through a pad of silica gel, and rinsed with CH_2Cl_2 (50 mL). The solvent was removed under reduced pressure, and the crude residue was chromatographed on silica gel (10:1 hexane/ $EtOAc$ eluent) to afford 232.2 mg (89%) of 2-methyl-1-(triethoxysiloxy)cyclopentane.

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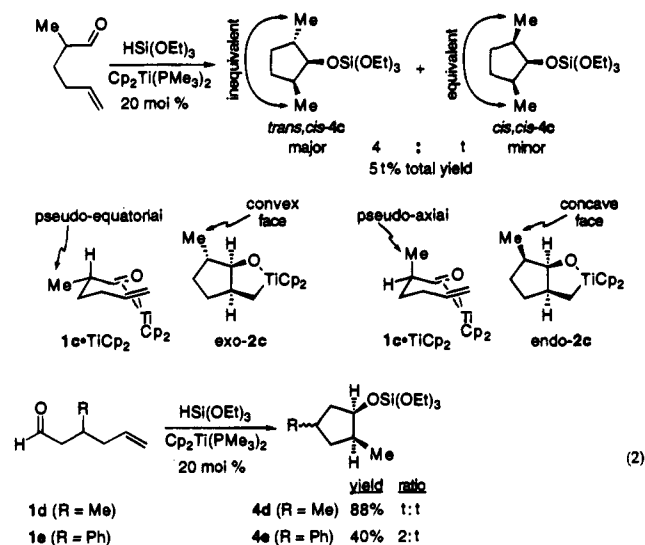
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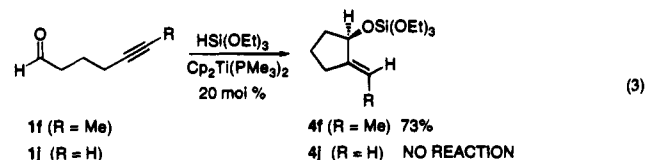
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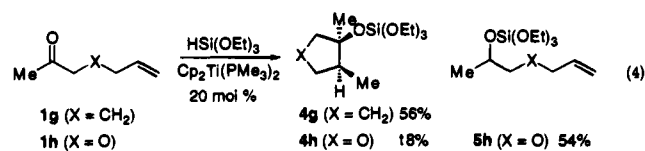
Scheme 3



Catalytic reductive cyclization of internal alkyne **1f** proceeded cleanly while a similar reaction of the corresponding terminal alkyne **1j** did not proceed at all (eq 3). Terminal alkynes have been noted to be problem substrates in related reductive cyclization reactions.^{1a}



Ketones **1g** and **1h** were also subjected to the catalytic reductive cyclization protocol (eq 4). Ketone **1g** cyclized cleanly to give **4g**. Ketone **1h**, however, gave a ca. 1:3 mixture of cyclization product **4h** and ketone reduction product **5h**. Although metallacycle formation and subsequent silane-induced cleavage proceeded cleanly for both ketones when the reactions were performed stoichiometrically, ketone reduction was a significant side reaction for **1h** under catalytic conditions.



The different behavior of **1g** and **1h** might be attributed to diminished basicity of the olefin in **1h** resulting from the allylic oxygen in its tether. The weaker olefin ligand in **1h** might slow down metallacycle formation, allowing simple ketone reduction to become a competing reaction. Another possibility is that

the tether oxygen renders the ketone π system more electron deficient and thus more prone to reduction. Reduction without cyclization (e.g., **1h** \rightarrow **5h**) is also a competing side reaction encountered in all catalytic reductive cyclizations run with less than 20 mol % titanium catalyst. The mechanistic basis for the relationship between catalyst stoichiometry and cyclization/reduction selectivity is unclear at this point.

In summary, we have reported titanium-catalyzed carbonyl-olefin and carbonyl-alkyne reductive cyclization reactions related to the stoichiometric reactions first reported by Whitby and Hewlett. The cis selectivity of the carbon-carbon bond forming reaction is complimentary to the trans selectivity obtained in related samarium-mediated cyclizations reported by Molander.⁹ Both ketones and aldehydes are good substrates for the titanium-catalyzed reductive cyclization reaction. Previously developed reductive cyclization protocols are largely limited to ketone substrates.^{9,10} Reductive coupling reactions of chiral metallocenes should proceed with high levels of asymmetric induction.¹¹ This idea, however, remains largely untested^{12,13} since the stoichiometric nature of most of the methods reported to date renders asymmetric processes impractical. With the development of a catalytic procedure, a practical asymmetric reductive cyclization reaction can now be envisioned. Efforts to develop such a reaction are currently in progress.

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Supplementary Material Available: Experimental procedures and spectral data for all compounds (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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